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Abdominal Manifestations of Sickle Cell Anemia
The Role of Bacteria in the Gastrointestinal Tract with Changing Concepts of Intestinal Function
The Status of Liver Biopsy
Diaphragmatic (Hiatal) Hernia
Cricopharyngeal Achalasia
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Carcinoma of the Pancreas
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The Efficacy of Dihydroxy Aluminum Aminoacetate in the Medical Cure of Peptic Ulceration

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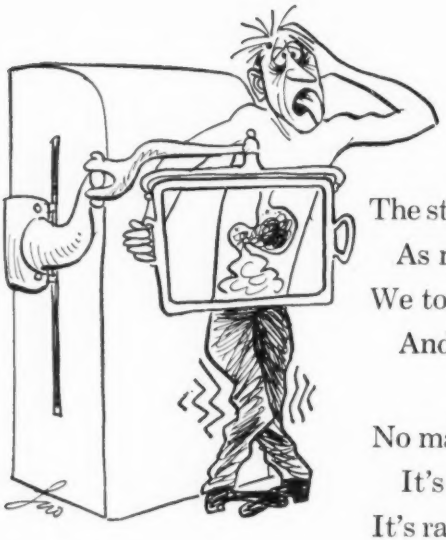

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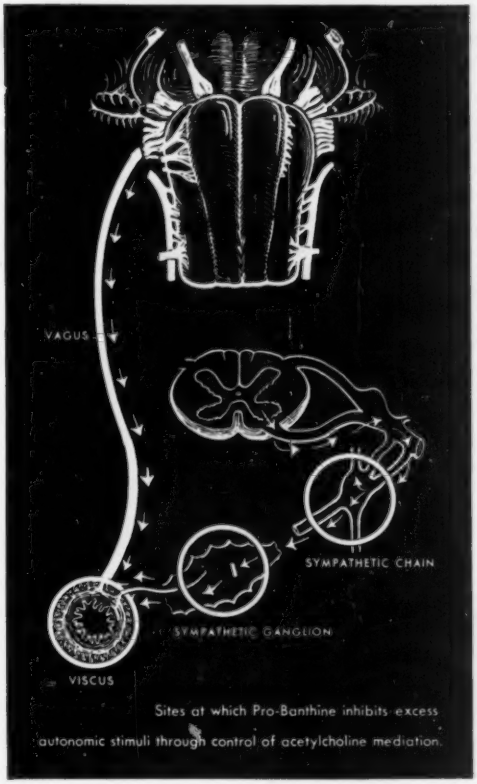

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2. Roback, R. A., and Beal, J. M.: Gastroenterology *25*:24 (Sept.) 1953.

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The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

contents:

Editorial Board and General Information 4

Abdominal Manifestations of Sickle Cell Anemia ... HENRY G. RUDNER, JR., M.D. and HENRY G. RUDNER, SR., M.D., F.A.C.P., F.A.C.G. 11

The Role of Bacteria in the Gastrointestinal Tract with Changing Concepts of Intestinal Function ..... KARVER L. PUESTOW, M.D., F.A.C.P., F.A.C.G. 22

The Status of Liver Biopsy ..... N. E. ROSSETT, M.D., F.A.C.P., F.A.C.G. 33

Diaphragmatic (Hiatal) Hernia S. L. STEPHENSON, JR., M.D. and E. L. POSEY, JR., M.D., F.A.C.G. 38

Cricopharyngeal Achalasia ..... JAMES T. NIX, M.D., Ph.D. (Surg.), F.A.C.G. 45

Functional Causes of Dysphagia JOHN M. MCMAHON, M.D., F.A.C.G., F.A.C.P. 51

Carcinoma of the Pancreas .... L. C. SANDERS, M.D., F.A.C.P., F.A.C.G. and ROBERT MCBURNEY, M.D., F.A.C.S. 59

The Importance of Proper Acid Neutralization in the Management of Gastric and Duodenal Ulcer ..... JACOB A. RIESE, M.D., F.A.C.G. 66

The Efficacy of Dihydroxy Aluminum Aminoacetate in the Medical Cure of Peptic Ulceration ..... MARION L. RICE, JR., M.D. 74

President's Message 83

News Notes 84

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Index to Advertisers

Ames Co., Inc. 10
Astra Pharmaceutical Products, Inc. 6
Brayten Pharmaceutical Co. 7
Burton, Parsons & Co. ..... 3rd cover
Ciba Pharmaceutical Products, Inc. 89
Coca-Cola Co. 92
Hoffmann-La Roche, Inc. 2
Horlicks Corp. 92
Lakeside Laboratories 96
Lilly, Eli & Co. 90
Organon, Inc. ..... 2nd cover
Pfizer Laboratories 9, 95
Rorer, Wm. H., Inc. 8
Searle, G. D. & Co. 1
Squibb, E. R. & Sons, Div. of Mathieson Chemical Corp. 6
Upjohn Co., The 93
U. S. Treasury 94
Warner-Chilcott Laboratories ..... 4th cover
Winthrop Laboratories 91

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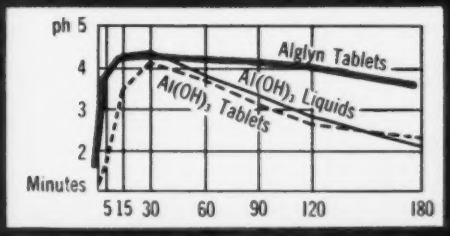

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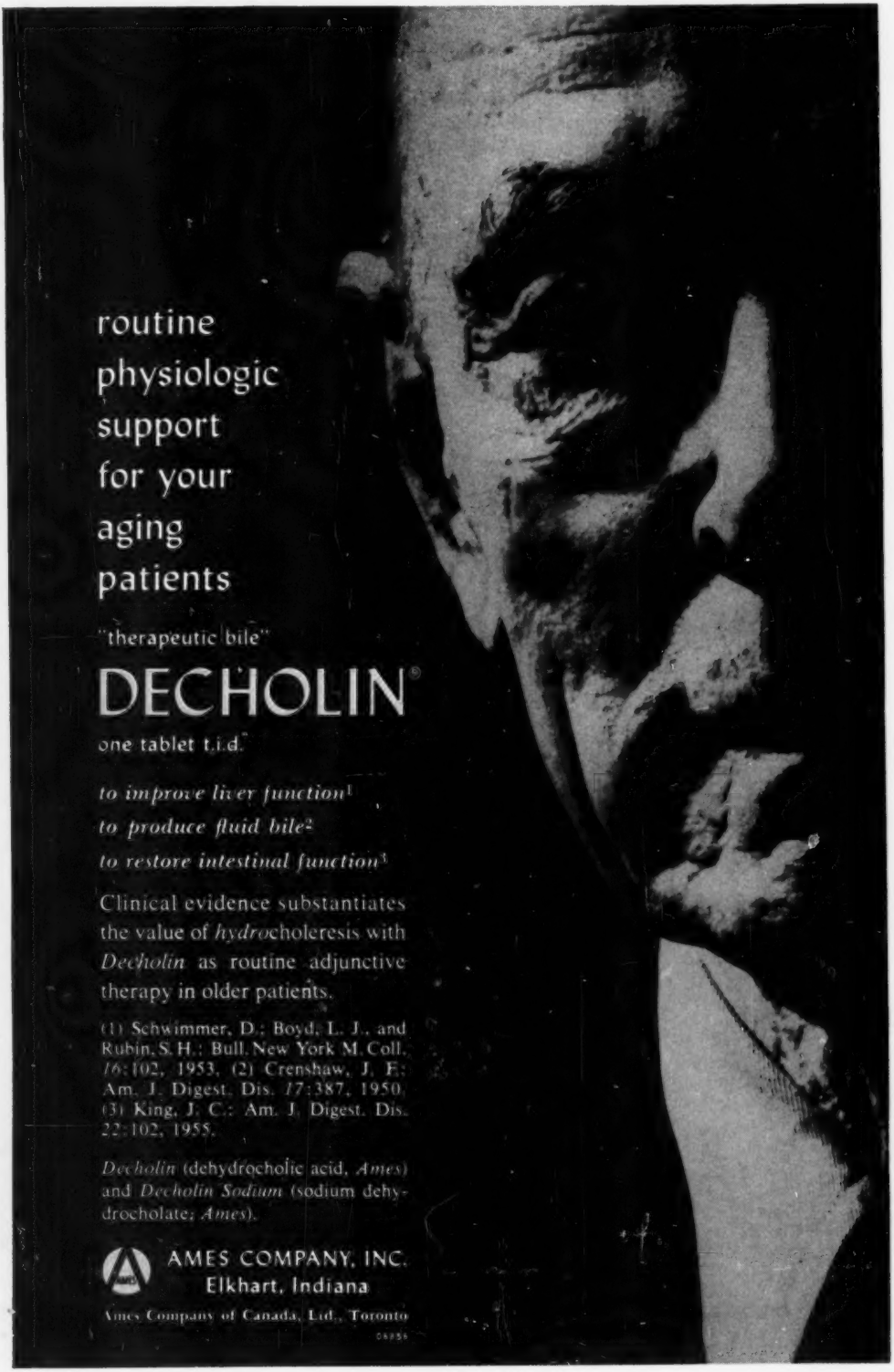
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ABDOMINAL MANIFESTATIONS OF SICKLE CELL ANEMIA*

HENRY G. RUDNER, Jr., M.D.

and

HENRY G. RUDNER, Sr., M.D., F.A.C.P., F.A.C.G.

Memphis, Tenn.

The exact nature and cause of abdominal symptoms that occur in patients with sickle cell anemia present a special challenge to the hematologists, gastroenterologists and the surgeons. Persons with sickle cell anemia may feel perfectly well one day, and on the following day be seized with an attack of abdominal pain, nausea, vomiting, muscle spasm, fever, leucocytosis and jaundice.

The physician may be called because of the patient's acute abdominal pain. There is frequently an associated scleral icterus and the case may resemble gallbladder disease or right lower quadrant pain with muscle spasm, vomiting and fever suggesting appendicitis; so it is necessary for all of us to become aware of the abdominal manifestations that may be associated with sickle cell disease.

It is the purpose of this paper to discuss the abdominal symptoms of the disease and review some of the explanations which have been suggested to be responsible for these abdominal "crises".

DESCRIPTION AND INCIDENCE

Sickle cell anemia can best be defined as a familial and hereditary type of hemolytic anemia most always confined to Negroes. Credit for description of the first case of sickle cell anemia goes to Herrick, who in 1910 described "peculiar elongated and sickle-shaped blood corpuscles in a case of severe anemia"[1]. In 1934 the world literature on sickle cell anemia numbered about 80 articles. Since that time a large accumulation of work has been devoted

*Read before the Second Annual Convention of the American College of Gastroenterology, Chicago, Ill., 24, 25, 26 October 1955.

to the study of this disease. The pathological features have been described by Diggs and others[2].

Briefly, there are two varieties of sickle cell disease: 1. heterozygous form (sickle cell trait) generally thought to be nonsymptom-producing and 2. homozygous form (sickle cell anemia) the serious form, which is characterized clinically by symptoms of anemia, leg ulcers, jaundice, attacks of pain in the abdomen and extremities. This form causes a reduction in life expectancy, the majority of patients dying before the age of 30 years.

How common is sickle cell anemia in Negroes in the United States? It has been stated that the incidence of the trait (sicklemia) is from 7 to 10 per cent in certain localities and that 1 out of 40 Negroes whose red cells sickled showed evidence of sickle cell anemia[3].

The charts of 100 sickle cell anemia cases who were admitted to the City of Memphis Hospital because of sickle cell crisis have been studied and particular attention given to the most common signs and symptoms at the time of admission. Criteria of sickle cell crisis* consists of finding anemia, jaundice, abdominal pain, pain in extremities, anorexia, previous record of similar attacks, if available (Table I).

The Abdominal Crises

The exact nature and cause of the so-called abdominal symptoms are as yet unknown. Abdominal viscera most frequently involved are the spleen, liver and mesenteric lymph nodes; less commonly involved are the intestinal tract and gallbladder. One interesting form of abdominal crisis occurs as follows: Patients with sickle cell disease may develop splenic infarction on high altitude flights in aircraft that are not adequately pressurized. Left upper quadrant pain, nausea, vomiting and fever occur while in flight and surgery on these patients reveals massive necrosis of the spleen presumably due to hypoxia.

In most cases of sickle cell anemia, especially when jaundice occurs or there is evidence of sickle cell crises, the liver becomes enlarged[4,5]. Our series of 100 cases of sickle cell crises revealed 45 patients to have enlarged livers. Livers of these patients are usually tender and often there is an associated jaundice not of the obstructive type. It has been reported that with repeated infarction of the liver obstructive jaundice may occur. Cephalin flocculation determination is usually found to be positive and in a large percentage of patients an elevated urine and fecal urobilinogen are present. With jaundice the serum bilirubin is, of course, elevated and frequently both the one minute fraction and the total bilirubin readings are higher than normal; especially if there has been previous liver damage.

*Actually a crisis in this disease may be defined as any sudden change in the patient's course of an abnormal nature.

At autopsy, the usual description of the liver is gross enlargement and microscopically the sinusoids are distended with abnormally shaped red blood cells of many sickled forms. The central veins are distended and the Kupffer cells are enlarged and contain varying amounts of hemosiderin pigment. Advanced cirrhosis is usually not present, probably due to early death in most cases.

Infarction of the spleen, especially in the younger age groups has been suggested as a cause of left upper quadrant pain. The splenic pathology is

TABLE I

FREQUENCY OF SIGNS AND SYMPTOMS DURING SICKLE CELL CRISIS

Signs		Pain	
I. Scleral icterus (on admission)	50%	a) *Abdomen*	40%
II. Palpable		b) *Headache*	21%
a) Liver	45%	c) *Legs*	14%
b) Spleen	27%	d) Substernal	18%
III. Edema		e) *Low back*	13%
a) Feet	15%	f) Knees	13%
b) Eyelids	9%	g) Arms	9%
c) Hands	8%	h) Shoulders	9%
d) Arms	4%	i) Wrists	7%
e) Legs	2%	j) Multiple joints	6%
IV. *Anorexia*	25%	h) Ankles	5%
V. *Nausea or vomiting*	30%		
VI. Drowsiness	16%		
VII. *Fatigue*	13%		
VIII. Dyspnea	11%		
IX. *Chills*	9%		
X. Tachycardia	3%		
XI. *Convulsion*	3%		
XII. *Comatose*	3%		

Ten Most Frequent Findings

1. Scleral icterus
2. Palpable Liver
3. Pain in abdomen
4. Nausea, vomiting
5. Palpable spleen
6. Anorexia
7. Headache
8. Pain in legs
9. Substernal pain
10. Drowsiness

characteristic and consists of a series of progressive changes from congestive enlargement to fibrotic atrophy with the passage of time. Diggs and Ching have described the pathology as follows: "In early stages the spleen is enlarged and infarcts are common. The organ is firm, purplish brown in color. Lymphoid aggregates are small, germinal centers absent and capillaries distended with sickled cells. The pulp is also congested. In advanced stages the spleen is smaller, dull grey in color and bound by adhesions. Many areas of siderosis are present and there is much deposit of calcium, iron and greenish-yellow pigmentation"[2].

In sickle cell anemia as well as other hemolytic anemias, gallstones occur frequently and are usually of the calcium bilirubinate type and radioopaque. Weems reported gallstones in 12 out of 44 autopsy cases diagnosed as sickle cell anemia[7]. Diagnosis of gallbladder colic is frequently made and with jaundice, leucocytosis and fever, surgical exploration and removal of gallstones has been performed in the past with recurrence of symptoms following surgery.

Few consistent findings involving the stomach and intestines have been reported. Of course, these patients may develop peptic ulcers, intestinal obstructions or peritonitis which may not be related to their underlying disease. Since surgical intervention frequently is accompanied by a difficult postoperative course and occasional unexplained sudden death, it is important to understand that sickle cell crisis with abdominal symptoms can imitate almost all acute surgical emergencies involving the abdomen.

It becomes evident that involvement of the abdominal viscera discussed above could not explain adequately and consistently the various symptoms of an abdominal crisis mentioned. Many other ideas on the subject are noted in the literature.

In 1931 Yater and Mollari felt arterial thromboses played a part in the abdominal symptomatology of one case[8]. In 1932 Leivy and Schnabel called attention to the compression of the vertebrae in the thoracic and lumbar region and considered radicular type pain with abdominal radiation as a cause[9]. Murphy and Shapiro believed that the pain could be due to vascular occlusion and associated thromboses. Sydenstricker, Mulherin and Houseal believed splenic hemorrhage caused abdominal pain in many of the patients and reported this finding in 1923[10]. Mesenteric and retroperitoneal adenitis were found consistently enough at autopsy to be reported by Crastnopol and Stewart in 1948 as a cause of abdominal symptoms[11].

Diagnosis

It should be remembered that sickle cell anemia is a chronic disease. Symptoms first appear in infancy and are associated with periods of excessive blood destruction and jaundice of a hemolytic type. As these patients grow older they frequently are mildly anemic and jaundiced but seem to adapt to this state. Often hemolytic anemias are described by the phrase "more yellow than sick". Added to this picture are acute attacks of abdominal pain associated with rheumatoid manifestations and fever.

A severe case with "crisis" appears quite ill, often "doubled" with pain frequently generalized over the abdomen. Rigidity of abdominal muscles are, in our experience, not characteristically found, although with severe attacks there may be muscle spasm, fever, nausea and vomiting and leucocytosis. Pain is usually in the midline about the umbilicus but may be in any of the abdominal

quadrants. The type of pain varies from colicky to dull and aching and it is easy to understand where mistaken diagnoses of acute appendicitis, acute cholecystitis, intestinal obstruction or perforating peptic ulcer are made.

It is valuable to have a history of similar episodes, as these, in the patient's past history. Often it is difficult to decide what course to follow after the presence of sickle cell anemia has been established. Patients with sickle cell anemia can develop the usual abdominal symptoms and diseases that all other patients develop, which make the differential diagnosis more complicated.

The most valuable tool in diagnosis is the finding of sickled red blood cells in the sealed moist blood preparations.

The following is the report of a representative case admitted with the diagnosis of sickle cell crisis with abdominal complaints terminating fatally. Autopsy findings are included.

Case Reports

Case 1:–Sickle cell anemia was diagnosed on previous admissions. Most admissions were for extreme pain in the abdomen and extremities.

W. P., 5½ years, colored male, last admission to the City of Memphis Hospital was because of pain in the perumbilical area for eight hours' duration. Pain began at 2:00 A.M. and patient was unable to fall asleep because of the severity and constant nature of the pain. There were fleeting pains in the legs and fever was present.

Physical examination:–Pulse 148, respiration 20, temperature 100°, weight 31 lbs. General appearance was that of a well developed and fully nourished 5½-year old colored male complaining of pain in the abdomen. Some rhinorrhea was noted. Lungs were clear and resonant. The heart was negative, except for a slight roughening of the pulmonic first sound. Examination of the abdomen revealed the spleen to be barely palpable. Remainder of the examination was essentially negative.

Clinical Impression:–Sickle cell anemia and possible rheumatic fever.

Laboratory:–R.B.C. 2,030,000 per cu. mm., W.B.C. 6,420, per cu. mm., hemoglobin 9 gm.

Sickle cell trait confirmed by laboratory. Urine was essentially negative. Sedimentation rate was 23 mm. in one hour.

Course in hospital:–Two days after admission to the Hospital, the patient became quite dyspneic, respiration became rapid and labored. Extremities were cold. Pain in the upper abdomen became severe and the patient "begged" for something to ease the pain. The patient was placed in an oxygen tent and was being typed for blood transfusion when he suddenly expired.

The chief complaint on admission five times previously was because of abdominal and joint pains. Surgical consultation was requested because of the severity of the abdominal pain; but the consultant wisely believed the pain was due to sickle cell crisis and not an acute abdomen. Blood transfusions on each admission improved symptoms until the last admission.

Autopsy findings on the heart revealed no gross abnormalities. Lungs appeared to be slightly congested. Peritoneal cavity negative. Stomach, duodenum, gallbladder were not remarkable. The liver was not enlarged. The spleen was enlarged and firm. The rest of the organs showed no gross abnormalities. Microscopic examination showed the following:

Spleen:—Pulp congested with sickle cells. Numerous malpighian corpuscles had been replaced by fibrous connective tissue and filled with green granules. These were shown by iron stain to be deposits of that metal. No infarcts were noted. Tissue diagnosis—siderofibrosis of spleen.

Lungs:—Tissue diagnosis—mild pulmonary edema.

Liver:—Section showed congestion of capillaries with sickled cells. Brown pigment granules were noted within the Kupffer cells. Tissue diagnosis—siderofibrosis of node, early.

Intestine:—Not remarkable.

Final anatomical diagnosis:—1. Sickle cell anemia, 2. Siderofibrosis of the spleen and mesenteric lymph nodes, 3. Hemosiderosis of the liver, 4. Mild pulmonary edema.

This case demonstrates one of the most puzzling problems of the pathogenesis of a case of sickle cell anemia in crisis and ending with sudden and unexplained death.

None of the findings at autopsy could adequately explain why this patient had such severe abdominal pain and no absolute mode of death could be found. It would seem necessary to look further into this problem and suggest other explanations for the bizarre and often critical course of the abdominal crisis.

Case 2 is interesting because once again there was abdominal pain, sickle cell crises ending in sudden death. He was found to have a duodenal ulcer which could have caused some of the symptoms of abdominal distress. This again reminds us that patients with sickle cell anemia and abdominal crises may also have other disease of the abdominal viscera.

Case 2:—C. C. was a 30-year old colored male whose last admission to the City of Memphis Hospital was in 1954 because four weeks prior to admission marked jaundice and dark urine was noted. Three weeks before there was

recurrence of severe joint pains in knees and ankles, five days previously he complained of occipital headache, upper abdominal pain, low back pain and swelling of ankles.

There were also complaints of flatulence and nausea, fatigue and frequent bouts of epistaxis.

His past history revealed that a gastrointestinal series five years previously showed a duodenal ulcer to be present. At that time he complained of epigastric pain, nausea and vomiting between and after meals.

Physical examination on readmission revealed a jaundiced colored male with a temperature of 100.4°, pulse 108, respiration 24 and B.P. 120/80. Heart sounds were regular. There was a grade IV systolic murmur over the precordium and rales over both lung bases. The abdomen was not rigid, but some tenderness over epigastric region was noted. Liver, kidneys and spleen were not palpable.

The hospital course was progressively downhill. Therapy consisted of an ulcer regimen, antibiotics, and fluid and electrolyte therapy. After 24 hours in the hospital, the patient went into shock, failed to respond to 1,500 c.c. of whole blood and expired.

Laboratory reports:—Hgb., 7.84 gm.; R.B.C., 2.3 million; Hematocrit, 19 vol. per cent; M.C.V., 81 cu. microns; M.C.H., 33 micromicrograms; M.C.H.C., 42 per cent; W.B.C., 33,500 per cu. mm. Differential—N. Bands, 12 per cent; N. Segmented, 75 per cent; Lymphocytes, 6 per cent; Monocytes, 7 per cent; Reticulocytes, 21 per cent; R.B.C., 5 nucleated R.B.C./100 W.B.C.; 8 sickled cells/100 R.B.C.

Urine:—Glucose, negative; albumin, 2+; occult blood, negative; sp. gr., 1.017; pH, 7.0; urobilinogen, positive; bilirubin, 4+ (Fouchet's); microscopic—15-25 W.B.C./hpf, R.B.C.—too numerous to count.

Blood Chemistry:—Total protein, 6.2 gm.; albumin, 2.8; globulin, 3.4; serum bilirubin total, 14.6; N.P.N., 28 mg. per cent; Serological test for syphilis—negative.

Autopsy Report

The main findings at autopsy were in the duodenum, lungs, liver, spleen and kidney. The lungs were heavy and there was much edema fluid.

Microscopic examination revealed the capillaries to be engorged with agglutinative thrombi. There was no evidence of infarction or inflammatory reaction. Numerous sickled cells were seen in the arteries.

The liver showed an increase in fibrous tissue and bile duct proliferation which was interpreted as early cirrhosis. Cirrhosis was believed to be due to repeated injury to the liver, and subsequent repair. Present here also were the agglutinative thrombi and pigment laden macrophages.

The splenic pulp was completely replaced by fibrous connective tissue. This organ weighed only 4.2 gm.

A horseshoe kidney was present. No evidence of acute pyelonephritis was present. A marked prostatitis was found. The duodenum presented an ulcer

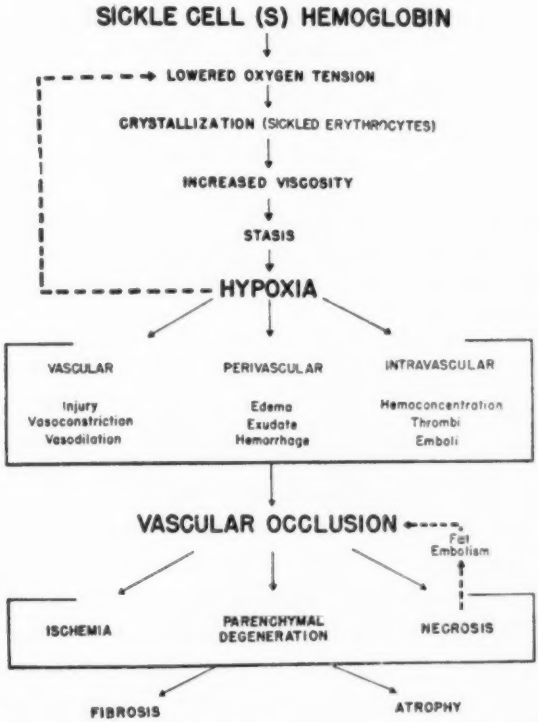

Fig. 1—Diagram illustrating a concept of the mechanism of vascular occlusive processes in sickle cell anemia.

with sharp edges and the base was green. This was a peptic ulcer and was apparently still active.

Comment

The abdominal distress seen in sickle cell anemia is undoubtedly due to several factors. The following diagram suggested by Vorder Bruegge and Diggs

summarizes the vascular occlusive phenomena which accounts for some of the symptoms (Fig. 1).

It is our impression that another factor plays a most important part in the production of sickle cell crisis and accounts for many of the symptoms and events of all hemolytic anemia which heretofore have not been understood.

During the course of all hemolytic anemias iron is released from the red blood cells at varying rates. When the iron binding capacity of siderophilin (the transport form of iron) is exceeded then toxic symptoms occur[12]. These toxic symptoms after injection of iron intravenously have been described by Goetsch, Moore and Minnich[13] as follows:

Shortly after intravenous injection of large amounts of colloidal ferric iron (0.608 to 1.32 gm.) is begun, the patients began to complain of nasal stuffiness, headache, lacrimation, a desire to sneeze, paresthesia, nausea, vomiting, diarrhea, abdominal or low back pain, tachycardia and transient fall in blood pressure. Shortly after injection, usually chills and fever occur and on the following day profound weakness. In severe reactions, convulsions and a comatose state may occur.

We believe the similarity of these symptoms and those that occur during a hemolytic sickle cell crisis is more than coincidental (See italicized findings in Table I).

Some known facts concerning iron metabolism that strengthen this hypothesis are that in hemolytic anemias, the serum iron binding protein (siderophilin) is almost completely saturated with iron from hemolyzed erythrocytes[13]. This would explain why the depot iron fraction (storage form in tissues) is increased. Most of the iron liberated at the destruction of red blood cells is rapidly taken up again in newly formed red blood cells. Thus, most iron runs through the cycle: hemoglobin > depot iron > serum iron > depot iron > hemoglobin. If the red cells are destroyed more rapidly than they are regenerated (sickle cell hemolytic crisis), a part of surplus iron is deposited in iron depots in the reticuloendothelial tissues in the form of ferritin. It is mainly stored in the liver, spleen, bone marrow, ovary, testicle and kidney.

Holmberg and Laurell found that intravenous injection of iron into patients with hemolytic type of anemias and especially pernicious anemia was followed by symptoms of intolerance even after as little as 2 mg. were given[14]. This could explain some of the symptoms of abdominal pains, nausea, etc., without severe anemia or a hemolytic process in sickle cell disease. It would apparently take very little to tilt the balance between the iron saturation limit of the serum and level of serum iron. Many factors must operate to keep this balance. It has been shown experimentally by Laurell that in patients with hemolytic anemias the values for the saturation limit are lower than normal[15].

Possibly in these diseases there is a defect in iron metabolism as well as in the red blood cells.

Other factors that are involved are the effects of the pituitary adrenal axis on regulating the level of serum iron. Cartwright has shown that the adrenal cortex when activated by the pituitary causes changes in the serum iron level under conditions of stress[16].

Further studies on the subject will be reported in a subsequent publication.

Summary

1. The signs and symptoms of 100 cases of patients with sickle cell crisis are evaluated.

2. A discussion of the abdominal manifestations of the disease are noted with a description of the types of abdominal pain and accompanying jaundice, fever, nausea and vomiting, leg pains and leucocytosis.

3. A review of the literature for an explanation of the abdominal crises is made and several factors seem to be invloved including vascular occlusions in the abdominal viscera.

4. Two cases of abdominal crisis with death and autopsy are reported.

5. Since there has been no conclusive evidence of the cause of the abdominal symptoms and other symptoms of sickle cell crises; a new hypothesis is suggested. This explains the headache, abdominal pain, chills, fever, nausea and vomiting to be due to the heavy metal effect of iron. As new iron is released from red blood cells in such a fashion that the iron binding capacity of siderophilin (transport form of iron) is exceeded, toxic symptoms occur. These toxic symptoms are the same as those that occur in an abdominal sickle cell crises.

6. From the following it should be mentioned that promiscious iron therapy as a therapeutic procedure in hemolytic anemias is not only unnecessary, but contraindicated. It may well cause more tissue hemosiderosis than would ordinarily occur.

Conclusion

The abdominal crisis of sickle cell anemia presents a most dramatic picture. The signs and symptoms that occur have been presented with hopes that the disease will be considered more often when faced with the problem of an acute abdomen in a colored patient.

There is no specific therapy for the disease or for the abdominal crisis. Of course, supportive measures, transfusions and sedatives are often required to make the patient more comfortable. A good general rule to follow is watchful waiting when symptoms are difficult to explain. The patients with the

active form of the disease usually have a stormy postoperative course with recurrence of abdominal symptoms if they were due to sickle cell crisis alone.

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THE ROLE OF BACTERIA IN THE GASTROINTESTINAL TRACT WITH CHANGING CONCEPTS OF INTESTINAL FUNCTION*

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Introduction

In our efforts to provide better care for our patients, it is necessary not only to re-examine that which is old, for the old order changeth, but also to evaluate and accept that which is new. As contributors to the symphonic effort of medical scientists, both pre-clinical and clinical, we must include the findings of others in allied sciences and with different disciplines, viz., the biochemist and the nutritionist. The term, symphonic, is used, advisedly, since we must re-emphasize the fact that the science of medicine represents more and more the concerted efforts of men in many fields of research. Let us attempt to broaden the horizon of intestinal physiological concepts by pointing out, first of all, pitfalls in present practices, and secondly, by suggesting new, and in many instances, untried approaches to clinical problems.

Aspects of Intestinal Motility

For a long time efforts have been made to explain the motility of the intestines through the autonomic nervous system. These efforts have been largely futile. Motility of the intestines is not only essential to the propulsion of its contents but the various types of intestinal motility are conducive to better absorption. Failure of absorption, as in ileus, is only one manifestation of a failure of intestinal motility, whereas hypermotility conversely may not allow time for adequate intestinal absorption. Regarding this most necessary function of intestinal motility little is known of intestinal innervation. The gradually changing concept that the extrinsic sympathetics and parasympathetics are reciprocal in their relationship to each other and not antagonistic is alone evidence enough of our delay to utilize, in a practical way, the information given to us by the physiologist based upon the four technics for studying intestinal motility: 1. "direct visualization 2. indirect visualization by the use of radiologic methods 3. the recording of the rate of propulsion of contents 4. the recording of changes in pressure or volume in the intestinal lumen"[1].

The importance of the contents itself as passenger in affecting intestinal motility must be emphasized because of its physical, chemical, bacteriological, and volumetric qualities. Hence, there is a necessity for giving further consid-

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eration to the nature of the intestinal contents. When a better conception of normal intestinal motility is available we will have a better understanding of disturbed motility in disease.

Role of Roughage

Bacterial residues account for a large proportion of the mass of dry feces; the trend of large fecal outputs parallels large bacterial weights. Studies on the human by Williamson and Parsons[2] limited to the factors influencing the fecal elimination of thiamine demonstrate the effects of large amounts of plant fiber in increasing the bulk of stool. They point out that the bulk of feces is determined by the number of bacteria. Furthermore, the increase in bulk is far greater than can be accounted for by the actual amount of fiber by dry weight. Therefore, pulp stimulates bacterial activity to account for the increased bulk, and the measurement of thiamine excretion may be used as an indirect method of measuring bacterial activity. At the same time, they have demonstrated that the fiber does not interfere with absorption, even though the stool contains much intact fiber. They note that the length of time of passage and the moisture content have no effect. Water, sugars, and other soluble substances along with cellulose, however, create a favorable medium for synthesis by encouraging bacterial growth. Cellulose is not an inert material simply supplying bulk but their work suggests that its fate, along with other complex carbohydrates, may be determined by bacterial flora. Other observers have shown that almost all, if not all, of the vitamins of the B-complex are synthesized in a similar manner[3].

By the suppression of the bacterial flora of the intestines the volume of stool will be diminished. If at the same time a low-residue diet free from vegetable or fruit fiber is fed and an antibiotic suppressing especially the coliforms is given, the fecal stream is reduced to a small liquid mass. To the surgeon, the practical value of a combined preoperative regimen combining a low-residue diet with antibiotics is that preoperative purgation becomes unnecessary and an anastomosis of the intestines may be performed without the use of obliterating and traumatizing clamps. As Poth and associates[4] have demonstrated on the descending colon in 16 dogs with the use of sulfasuxidine the coliform count promptly diminishes and healing occurs by primary intention in a contaminated field without evidence of infection following end-to-end anastomoses. Rowe and associates[5] in their studies on the human have confirmed this report.

Significance of Bacterial Flora in Intestinal Function

Most additions to our knowledge of the role of intestinal bacteria in the physiology of nutrition and to our understanding of nutritional diseases have been obtained by indirect biochemical studies. Useful has been the clinician's direct approach in his studies of the stool for the detection of infestations and

the culturing of specific infections such as those causing the bacillary dysenteries, the Salmonella and streptococcic infections. These technics of direct observation and culture, however, have not been helpful in gaining an understanding of disturbed intestinal function in nutritional diseases or an understanding of such unsolved problems as chronic ulcerative colitis or sprue.

Likewise, culture media will probably never be developed to provide all of the nutrient requirements of a normal intestinal flora. It would be even more difficult to develop media to produce the pattern of flora in disease. The bacteriologist has interested himself more in the physiology of bacteria than in the physiology of the gastrointestinal tract.

By his indirect approach, the biochemist on the other hand, has not only clarified the nature of the pathogenesis of such diseases as pellagra, but he has also given us a wealth of information which we are as yet unable to translate into human utilization. He has furthered our knowledge of the mechanism of nutrition, the mechanism of development and the nature of some nutritional diseases, and even new diseases unknown or unrecognized have been produced. These diseases may be referred to as laboratory diseases. They are significant, however, in that they have anticipated the development of new clinical syndromes resulting from the changes in the bacterial flora of man by the use of antibiotics. Subsequently, we are beginning to see, clinically, new syndromes resulting from alterations effected by the use of antibiotics. In an age when the human diet is highly processed, changes of the intestinal flora may be expected. The biochemist has determined multiple effects of diet on intestinal flora and the role of bacterial flora on nutrition. From this approach he has demonstrated the effects of antibiotics on intestinal flora and in turn on nutrition.

The intestinal tract may be considered as a long *in vivo* test tube; in fact, we may look upon the intestinal tract as a series of multiple test tubes, for the bacterial flora varies at different levels, and flora which is normal at one level may be pathogenic at another. We have little information on the effect which bacteria high in the intestinal tract have upon synthesis, destruction, and absorption of nutrients. There is evidence to suggest that the greatest bacterial activity occurs in the cecum[6]. It is probable that little absorption of synthesized vitamins takes place in the colon below the cecum[2]. The function of the colon may be limited largely to the absorption of water so that a high fecal vitamin assay may not denote a high vitamin absorption, for the vitamins may be synthesized below their level of absorption.

Much of the information already available is only of academic interest, for as yet we have not learned to apply clinically that which is available from the laboratory. It is known, however, that "organisms may synthesize or destroy nutrients, produce or destroy toxins, or even alter digestion"[3].

It is not pertinent to this discussion to present the significance of all the known interrelationships in human nutrition or to attempt to infer all clinical applications which might be derived from experiments on animal nutrition. With the multiplicity of synthetic abilities of many organisms, with variations in absorption and with alterations in metabolism, which can be effected not only by antibiotics but by variations in the diet, the complexities of intestinal nutrition are manifold. Isolated experiments, both with humans and animals, suggest similar results. In answer to the objection which might be raised that the results of animal experimentation are not applicable to the human, one must bear in mind that even though nutritional requirements vary from species to species there is a remarkable qualitative similarity in requirements. Not only in the field of biochemistry but in the field of plant pathology as well, scientific advances applicable to clinical medicine have antedated clinical observation. A mere sampling of observations made in the laboratory should suffice to suggest the immense amount of information which eventually should become available to the clinician.

Synthesis of Nutrients

The role of a complex carbohydrate, cellulose, has already been partially demonstrated by the synthesis of thiamine in the human[2]. There is ample evidence that almost all, if not all, of the vitamins of the B-complex are synthesized by the bacteria of the intestinal flora and in some instances in adequate amounts for human needs[7]. As early as 1926 Fredericia[8] demonstrated that Vitamin B deficient rats made spontaneous recoveries on uncooked starch. This phenomenon he referred to as "refection", meaning to restore. By comparison with man the rat has a relatively deficient flora. This suggests even a greater synthesizing ability in the human, but coprophagy in the rat may compensate for this difference. Stunted growth is one of the characteristics of vitamin deficiency in animals. Conversely, as will be noted later, alteration of the intestinal flora by the use of antibiotics may stimulate growth in growing animals[9]. Selective inhibition of competitive bacteria or by the increase of metabolic stimulators may explain this situation. The commercial implications of this observation are already abundantly manifest especially in the chicken and hog raising industries. Detergents recently have been demonstrated to have similar growth-producing propensities, and, being cheaper, may replace antibiotics in animal feed[10].

Garber[11] and associates have shown that ingestion of live baker's yeast interferes with the absorption of thiamine by human subjects and, to a lesser extent, interferes with riboflavin absorption. In the competition of the intestinal tract with live yeast there is presumably almost complete failure of absorption because of competition between the absorbing membranes of the yeast cells and the digestive tract with a resulting retention of the absorbed thiamine within the cell. So avid is the yeast cell that pure thiamine hydrochloride

ingested with fresh baker's yeast is not recoverable in the urine. "Nutritional dry yeast", however, will yield both its thiamine and riboflavin along with other factors in the body[11].

The relationship between vitamins and amino acids is well illustrated in the experiments by Elvehjem[7] and his co-workers in their establishment of the pathogenesis of pellagra. Corn is not only deficient in tryptophane and niacin but it so reduces the synthesis of niacin as to produce a deficiency. Tryptophane, an essential amino acid, responds exactly in the same way as niacin. With adequate niacin tryptophane is spared to be used as an amino acid, but with a deficiency of niacin it is synthesized from tryptophane. The converse is true to the same extent, so that available niacin will synthesize tryptophane in the absence of tryptophane. Under optimum conditions niacin synthesis can be as much as 100 times the amount ingested[12]. Lactose and milk will increase the synthesis of niacin and folic acid and niacin in excess increases folic acid[13]. Folic acid in turn will cause an increase in niacin. The addition of corn to a synthetic ration will reduce niacin excretion from 100 times the intake to 3 times the intake. Then, if thiamine is added, the niacin excretion will be increased to 5 times the intake[7]. Under aerobic conditions incubated feces removed from the human cecum will synthesize nicotinic acid, whereas under anaerobic conditions nicotinic acid will be destroyed[6].

A similar reciprocal relationship exists between folic acid and biotin as between niacin and tryptophane, for in deficiency states the addition of either one will cause a deficiency of the other. Folic acid will be synthesized on a diet high in carbohydrates[3]. With sucrose, vitamin requirements are highest. The order of importance of favorable effects of carbohydrates on vitamins is: dextrins, starch, lactose, glucose, and sucrose. In the human it is known that paraaminobenzoic acid, biotin, folic acid and pantothenic acid may be synthesized adequately. Less than adequate synthesis is probable with thiamine, riboflavin, pyridoxine, and nicotinic acid[14].

Dietary Fat

Dietary fat has an added importance. It supplies calories for energy and aids in the utilization of calcium and phosphorus. It probably assists as a carrier in the absorption of fat-soluble vitamins and is required for fertility, pregnancy, and lactation. It also is interrelated to other food substances; it spares them and alters metabolism. Optimum levels to supply essential fatty acids have been estimated to be equivalent to 25 or 30 per cent of the daily intake. High-fat diets may increase Vitamin B-complex requirements. Twenty-eight per cent fat causes a reduction of riboflavin and a decrease in cecal coliforms. Oleic acid is essential for folic acid synthesis. Fat spares thiamine. Polyneuritis with a thiamine-deficient diet, however, will develop more readily on a high-fat intake than on an isocaloric, carbohydrate diet. Acrodynia is related to pyri-

doxine deficiency with the omission of fat. Rancid fat destroys Vitamin A. Nicotinic acid deficiency is more readily produced on a low-fat diet. A more rapid fatty infiltration and necrosis of the liver with frequent hemorrhagic degeneration of the kidney occurs on a high-fat diet with a deficiency of choline and labile methyl groups[15].

Antibiotics and the Intestinal Flora

The first evidence of beneficial effects on metabolism from the use of an antibiotic was in 1946 with the demonstration of an increased growth response in the chick by Moore, et al[9]. They showed that sulfasuxidine and streptomycin alone or in combination will produce a marked reduction of the coliforms of the cecum. These drugs alter the intestinal flora with a change in the synthesis of vitamins by bacteria. They increase the dietary vitamin requirements or establish new requirements. They increase the folic acid requirement three-fold, and possibly may inhibit bacteria-producing toxins or render certain vitamins unavailable. As already noted the commercial implications of these observations are presently being capitalized on by the agriculturist in his feeding of animals in preparation for market. Dosage requirements for these purposes are far below those used currently in human therapeutics.

In human observations succinylsulfathiazole reduces nicotinamide. Aureomycin is most effective in removing Gram positive bacteria from the intestinal tract of man. With its use, however, there is a disturbance of balance with a flourishing of yeast and the development of new clinical syndromes. Acetylated sulfonamides will reduce the average fecal coliform count by 99.99 per cent in 3½ days and maintain this level, whereas with streptomycin, which initially is equally as effective, the reduction cannot be maintained. In preoperative preparation, therefore, streptomycin either alone or with sulfonamides has no value[4]. Reduction of the coliform count fails to reflect accurately the total colonic bacterial population including many important pathogens.

Paraaminobenzoic acid will counteract the effects of sulfaguanidine[16]. Succinylsulfathiazole will prolong bleeding time which can be corrected with Vitamin K[17]. Sulfasuxidine may repress granulocytes and erythrocytes with correction by the administration of liver. The sulfonamides reduce the coliforms and lactobacilli along with enterocoli and yeast forms, but with the addition of aureomycin, yeast forms increase. Aureomycin promotes yeast growth and, as already noted, yeast competes with the bodily processes and requirements. Growth promotion by antibiotics in experimental animals may be due to the elimination of competitors or favor the synthesis of growth-stimulating vitamins. The antibiotics used commercially in feed for hogs and poultry include terramycin, penicillin, aureomycin, and bacitracin[19]. The effects include improved health and lower mortality, and better food efficiency.

Sulfonamides decrease coliforms and lactobacilli. They cause a decrease in cecal and liver folic acid and biotin deficiency in rats. With their use there is a decrease in niacin and a compensatory increase in the size of the cecum. They prevent folic acid stimulation of niacin synthesis. Without folic acid they induce poor growth and agranulocytosis and reduce the volume of stools.

Antibiotic Effects on Pathogens

From the data discussed so far the wide diversity of effects on the normal intestinal flora, both beneficial and deleterious, are evident. Different antibiotics have different specificities of action and similar actions cause different bacterial responses. Although many organisms are affected, not all are affected similarly. Wide variations of therapeutic efficacy may be explained in part by the multiple factors involved, such as a lack of specificity of an antibiotic, the effects of the antibiotic on vitamin synthesis and breakdown directly or through the intermediate of the intestines. The intestinal tract contains a culture medium for pathogens, as well as normal inhabitants, and fluctuations in it may affect growth of pathogens as well as the normal inhabitants. Nothing is known, however, of how changes in the flora affect the pathogens, as nothing is known of symbiotic relationships between pathogens and normal flora. Just as antibiotics affect the biology of nutrition, so they may affect the metabolism of pathogens.

A case in point pertains to the prompt and complete eradication of *Enterobiasis Vermicularis* (pinworm) by the use of terramycin[20], which demonstrably also has an effect on the intestinal flora. It is conceivable that terramycin might act either by its direct effect on the female gravid pinworm and eggs or indirectly through an effect upon the bacterial flora, which in turn secondarily might account for the eradication of the infestation. The observed effects were in the immature embryos and eggs with ultimate disappearance of eggs. Other examples of the effects from the use of antibiotics may be cited. Aureomycin may have a favorable effect upon ulcerative colitis[21]. The effect may be to reduce secondary infections in mucosal erosions[22]. Salmonella enteritis has been difficult to evaluate[23]. The broad spectrum antibiotics, terramycin, aureomycin and chloramphenicol, however, have been remarkably effective in relieving symptoms, even of the worst types, of bacillary dysentery in Korean prisoners[24]. They have been equally effective against amebic dysentery. Terramycin alone so far has been credited with approaching 100 per cent effectiveness in amebiasis[25]. The mode of action is suggested as being antiamebic and an antagonistic action to associated microbial flora. The superiority of terramycin to other antibiotics may be due to its antibiotic potential or to the fact that it may be more polyvalent. *E. coli* serotypes have been demonstrated to be the cause of infantile diarrhea, which may be favorably affected with one of the three broad spectrum antibiotics[26]. The infection may be due to an extension

upward, or the pathogens may be airborne. Typhoid and paratyphoid fevers may be suppressed rather than cured[27,28].

All specific infections do not respond to antibiotic therapy, notably whipworm and hookworm[20] and strains of Salmonella. On the other hand, the treatment of perforated peptic ulcer may become a medical rather than a surgical problem, for treatment with penicillin, streptomycin and sulfadiazine in conjunction with continuous gastric decompression has been effective, with a zero mortality rate[29].

A few examples will suffice to demonstrate the untoward effects of floral alterations from antibiotics in therapeutic dosage. Aureomycin especially promotes moniliasis and causes an aureomycin diarrhea, with resulting inflammation from infection, sensitivity reactions, and Vitamin B avitaminosis. The manifestations include glossitis, stomatitis, pharyngitis, esophagitis, gastritis, colitis, and proctitis[30].

Anaphylactoid reactions have been noted from penicillin, streptomycin, and dihydrostreptomycin[31]. Sprue-like symptoms with steatorrhea have been noted following antibiotic therapy[32]. These effects may be counteracted or prevented by the discontinuance of the antibiotic and the administration of crude liver extract and B-complex parenterally, for by mouth the intestinal culture medium would be enriched. Acidophilous milk and buttermilk have rectified the pruritus and burning following broad spectrum antibiotic therapy[33] and Dramamine has apparently had life-saving effects in anaphylactoid reactions[31].

A possible role for antibiotics in the prevention of hepatic cirrhosis of nutritional origin has been suggested by György[34] from his studies on rats. In his experiments he determined that rats fed a diet low in protein, high in fat, and free from choline developed fatty livers and cirrhosis, and that aureomycin and terramycin had a lipotropic effect. In humans it is suggested that B_{12}, which is choline-sparing, in addition to antibiotics, might be prophylactic. More striking, however, has been the recovery of patients from fulminating hepatitis[35] and hepatic coma[36] following the use of aureomycin. Even though the mode of action of the antibiotics is not understood the beneficial effect is through the intestines against a viral disease.

Gastroenterological Basis of Disease

Systemic manifestations of disturbed intestinal functions are as yet poorly understood. A few known disease entities and many syndromes with remote clinical manifestations point to the intestinal tract as the site of their origins. The gastroenterologist heretofore has interested himself primarily in diseases limited to the gastrointestinal tract with little consideration of its possible role in causing remote symptoms involving other parts of the body. Diseases such as pellagra, beri-beri, and other deficiency diseases are well established as

being intestinal in origin. The favorable response to Vitamin A therapy in many instances of cutaneous hyperkeratinization, juvenile acne, *keratitis pilaris*, and *pityriasis rubra pilaris* suggest the intestines as the site of origin; the clinical manifestations are limited to the skin. Primary Addisonian anemia has been established as being of intestinal origin since the time of Minot and Murphy. Other anemias are related to a deficiency of folic acid supplied through the intestines. Portal cirrhosis most certainly has its origin in the intestines. Multiple sclerosis, it has been suggested, may be an intestinal disease[37]. Investigators are pointing their attention in this direction in an effort to determine its etiology. Evidence points to disturbed metabolism in the interrelationship of fat and pyridoxine in the intestines as a cause of acrodynia[3]. Hemochromatosis is now known to be a gastrointestinal disease, unique in that in this condition there is an abnormally excessive absorption of iron from the intestinal tract with an inability to eliminate it. The result is that iron is deposited in the tissues. Reduced absorption, on the other hand, is illustrated by a case of chronic ulcerative colitis which we had in which we were unable to produce a hypoprothrombinemia with Dicumarol.

Conclusions

1. Just as the biochemist has developed new, unknown or previously unrecognized diseases in animals, so we now are beginning to see the development of new clinical syndromes from the alteration of normal intestinal contents, both from the use of highly processed foods and the use of antibiotics to alter intestinal flora.

2. The intestinal tract cannot be sterilized but the flora can be changed both favorably and unfavorably to the patient.

3. The intestinal flora promptly returns to normal after the eradication of disease or the discontinuance of antibiotics. This will account for the less disastrous results that have been noted from the use of antibiotics.

4. The need for new physiological and clinical approaches to be included in the clinical study of the gastrointestinal tract is evident. Either the bacteriologist should develop new approaches or the biochemist should become clinical.

5. Although the gastrointestinal tract has a high potentiality for the synthesis of vitamins, it is not adequate for the synthesis of all vitamins. Natural vitamins are still important and until our knowledge of nutrition is greatly increased the supplemental use of multiple vitamins, especially now with the universal use of vitamin-inhibiting or vitamin-destroying antibiotics, is necessary.

6. A constant need for the clinical interpretation of animal experimental data is evident. Animal experimentation, both in the laboratory and in practical agriculture, is producing a constant flow of scientific data, which contribute to

knowledge on the physiology and pathology of the intestines. The application of these data to clinical medicine holds considerable promise and should be a challenge to the clinician.

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THE STATUS OF LIVER BIOPSY*

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Hyman I. Goldstein[1] only recently deceased historian of this organization noted that Ange Gabriel Maximé Vernois discussed liver puncture biopsies in a thesis "*Du diagnostique anatomique des maladies du foie et de sa valeur au point de vue thérapeutique*", which was published in 1844 in Paris, France. My subject is at least 111 years old.

Lucatello[2] in 1895 again described diagnostic liver biopsies using needle and syringe aspirates. General interest was aroused in this field by the work of Iversen and Roholm[3,4] who used a transpleural approach to the liver through the 9th interspace in the right posterior axillary line. They used a needle with a circular cutting edge and a trocar. The specimen was retained by syringe suction. Earlier in 1928, Silverman[5] had devised and described a punch biopsy device which retained its specimen and was primarily intended for biopsying neoplastic tissue. Tripoli and Fader[6] on June 7, 1940, before the American Society of Clinical Pathologists, read a paper describing the use of a modification of a Silverman biopsy needle for diagnostic punch biopsy of the liver but used an anterior abdominal approach. Shortly after this report, the obvious occurred; the Silverman biopsy needle was used through a transpleural approach by several investigators and a safe method for obtaining punch biopsies of the liver was established. The procedure has proved to be hazardous only in the hands of unqualified and untrained personnel.

The indications for liver biopsies are:

1. Hepatomegaly of undetermined cause.
2. Splenomegaly and presplenectomy.
3. Differential diagnosis of parenchymal and obstructive jaundice.
4. Primary or metastatic neoplasm of the liver.
5. Hepatic cirrhosis: a. Diagnosis
   b. Follow course.
   c. Prognosis
6. Determination of status or progress of hepatitis. Study of "posthepatitis syndrome".

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7. Evaluation of therapy and research. In fatty infiltration, histologic improvement occurs without laboratory change. Malaria produces no primary hepatocellular disease.

8. Suspected or recognized systemic disease.

Infectious hepatitis	Erythema nodosum
Miliary tuberculosis	Early syphilis
Brucellosis	Beryllium poisoning
Hodgkins	Amyloidosis
Histoplasmosis	Tularemia
Infectious mononucleosis	Kala Azar
Coccidioidomycosis	Schistosomiasis
Blastomycosis	Gaucher's Disease
Leprosy	Hemosiderosis

This appears to be an imposing list. As familiarity with the procedure increased and results were evaluated it became increasingly apparent that liver biopsy should be utilized whenever organic disease was suspected and a diagnosis was not forthcoming.

The contraindications for liver biopsy are:

1. Uncooperative patient.
2. Low blood prothrombin, (50 per cent Quick or better) or other coagulation defect.
3. Infection RLL or pleura.
4. Peritoneal cavity infection.
5. Ascites. (Paracentesis first).
6. Chronic passive congestion.
7. Pneumoperitoneum.
8. Probable severe obstructive jaundice or severe jaundice.

Some of these are absolute and the others relative. The urgency of the need for diagnosis and the severity of the contraindications are the determinants. As in all good medicine, rational judgment is necessary.

Reactions encountered are:

1. Pain at entry site with right shoulder radiation.
2. Epigastric discomfort while needle is in liver. Warn patient.
3. Friction rub. Hours to 2 weeks.

4. Intraabdominal hemorrhage. Watch 24 to 48 hrs.

5. Intercostal vessel injury. Keep needle close to lower rib.

6. Pneumothorax. Blunt scalpel usually.

7. Severe apprehension associated with various nervous and hysterical manifestations.

8. Nausea, anorexia, and vomiting. Use freshly prepared procaine only. (?) Intraliver procaine.

9. Abdominal pain and board-like abdomen, 1 per cent.

10. Arterial hemorrhage due to stab wound.

11. Shock. (?) (Air Embolism. Procaine reaction.)

In no instance have we had to resort to surgery or transfusion. A Levin tube with Wangensteen suction and Demerol® sedation proved successful in the most stubborn cases.

Our method has differed little from most recent reports. At the Kennedy V. A. Hospital the procedure was done in a treatment room and the patient transferred to a litter and then to his bed. At Baptist, Methodist and St. Joseph's Hospitals, more recently, we have done the biopsy at the bedside and believe fewer reactions have resulted. The patient receives 50 to 100 mg. of Demerol I.M., 30 minutes prior to biopsy, preceded by a barbiturate, Seconal 0.1 gm. orally. Food is not usually withheld. With the patient supine on the edge of the bed nearest the operator, the skin of the lower right axilla is prepared with tincture of Merthiolate® and alcohol after draping. The area of greatest dullness is selected from the anterior to the posterior axillary line in the 8th or 9th interspace and novocaine is used. We have used 4 c.c. of 1 per cent novocaine, 1 c.c. for the skin and 3.0 c.c. for the chest wall and liver capsule. A Bard-Parker knife with a fresh sharp No. 11 blade is used to cut through to the pleura. The Silverman needle, with the inner split needle at the very edge of the outer needle, (obturator is not used) is then rapidly inserted to the desired depth. The outer needle is moved over it to completely enclose it. Both are then rotated a half turn to break off the "liver sliver" and withdrawn. The entire maneuver should take 3 seconds. During this time the patient holds his breath in expiration. After biopsy, an ordinary adhesive bandage is used for a dressing. The patient remains in the supine position for 15 minutes. He then may assume any horizontal position for 8 hours. If nothing untoward has occurred he is permitted out of bed.

The experience of the essayist consists of 648 consecutive liver biopsies done at the Kennedy V.A. Hospital by himself or under his supervision and in

private practice at Baptist, Methodist and St. Joseph's Hospitals. No fatality has occurred.

The diagnoses resulting from biopsy are:

Normal	152
Cirrhosis (Laennec's)	275
Cirrhosis (Biliary)	12
Fatty Metamorphosis	96
Hepatitis (Viral)	42
Obstructive jaundice	23
Hemachromatosis	7
Hepatoma	6
Cholangioma	1
Metastatic carcinoma	5
Boeck's sarcoid	2
Tuberculosis	2
Histoplasmosis	2
Hodgkins' disease	1
Granuloma (undetermined)	5
Amyloid disease	1
	648

In a series of 1,000 patients studied at Cincinnati General Hospital, in Dr. Leon Schiff's gastric laboratory, microscopic examination of needle specimens from the liver confirmed the clinical diagnosis in 49.2 per cent, corrected it in 24.7 per cent, were noncontributory to diagnosis in 16.6 per cent, misleading in 3.5 per cent and inadequate in 6 per cent[7]. A footnote indicates a death occurred after 1,114 biopsies from bile peritonitis in an elderly patient with common duct stones. Klatskin[8] has done approximately 1,300 liver biopsies in New Haven in the past seven and one-half years with only 1 fatality: a man with severe viral hepatitis who went into irreversible shock following a transpleural biopsy complicated by moderate bleeding that was proptly corrected by transfusion. He has had two serious reactions neither of which was fatal or required surgery: An obstructive jaundice due to pancreatic carcinoma which was complicated by bile peritonitis following a subcostal biopsy and a patient with Hodgkins' disease complicated by a massive hemothorax and subdiaphragmatic hemorhage. Leonard[9] at the Hartford Hospital, in Hartford, Conn. has done more than 500 liver biopsies in the past five years on an out patient basis. The biopsy is done in the morning and the patient permitted to go home in the afternoon. He has done more than 750 biopsies on hospitalized patients with no fatalities in either group. He notes only one accident from which the patient had no symptoms: an assistant resident did a "low" transpleural biopsy and brought forth what proved microscopically to be kidney tissue.

The morbidity and mortality risks have been well-authenticated by Zamchek and Klausenstock[10] in their review of 20,016 needle biopsies which prove a negligible morbidity and a less than 0.1 per cent mortality rate.

Summary

Transpleural liver punch biopsy with a Silverman needle in the hands of personnel qualified by training and interest in liver disease, has provided a safe diagnostic modality in liver and other indicated systemic diseases. It has permitted earlier surgical intervention as well as the earlier institution of medical therapy. Its value is being repeatedly demonstrated as a research tool.

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DIAPHRAGMATIC (HIATAL) HERNIA*

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and

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In the past three years in our clinic we have seen hiatal hernia as a frequent clinical entity, particularly in the older age group. Some patients have been symptom-free, only having gastrointestinal studies as a part of a complete check-up at the patients' request. Others have experienced a plethora of abdominal and chest symptoms, the latter simulating coronary artery disease.

Valuable contributions to medical literature with entire studies on this subject have been made by Allison, Sweet, Harrington, Weintraub, Benedict and Gillespie, and others. We wish only to briefly review the subject of hiatal hernia in a busy gastroenterological practice. Emphasis is being placed on the finding of organic disease in patients who have previously been labeled as neurotic or "very tense persons unable to meet daily personal problems". In most instances anxiousness and tension were greatly relieved with the finding and treatment of hiatal hernia.

Incidence

From 1908 through 1925, 30 cases of diaphragmatic hernia were diagnosed clinically at the Mayo Clinic, whereas from 1926 to 1941 this diagnosis was made in 600 cases[1].

Weintraub[2] states that the incidence of diaphragmatic hernia varies, depending on the report, from 1 to 12 per cent. Shatzki[3] reported an incidence of 3.5 per cent in 1,500 roentgenographic examinations of the gastrointestinal tract. Evans[4] reported that 213 diaphragmatic herniae had been found among 6,124 upper gastrointestinal x-ray examinations during 1950 at the New York Hospital. This was an incidence of 3.4 per cent. Nuzum[5] found 12.2 per cent of diaphragmatic herniae in 957 patients. Weintraub[2] believes that a strong factor in the difference in reported incidences is because of the work done by Johnstone and Jones, demonstrating that several examinations may be necessary to establish the presence of a hernia. Also, unquestionably a dilated phrenic ampulla is occasionally called hiatal hernia due to difficulty in defining the collection of barium above the esophageal hiatus.

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Classification and Etiology

Kirklin and Hodgson[6] believe there are almost as many classifications as there are writers on the subject. We feel that there are two types of diaphragmatic hernia: The true diaphragmatic hernia and the hiatus hernia. The latter, which our cases demonstrate, is divided into 3 types, each being associated with an incompetent esophageal hiatus: Hernia due to congenitally short esophagus, the paraesophageal hiatus hernia, and the esophagogastric hernia. Bockus[7] favors this classification which he states was introduced by Åkerlund in 1926 although it erroneously includes the congenitally short esophagus as a type of hiatus hernia.

Now, however, what had previously been diagnosed as "congenital" short esophagus has been shown to be an acquired condition in a large proportion of cases[8]. Benedict and Gillespie, reviewing the work of others[8], state that the latter believe that lengthwise contraction of the esophagus follows irritation of the esophageal mucosa by gastric reflex. Thus, by the time the patient seeks advice, he may have an acquired short esophagus. Other causes of hernia are conditions with increased pressure in the abdomen such as pregnancy, obesity, ascites, and straining, and the wearing of tight garments. In some instances anatomical changes such as diminished elasticity of the diaphragmatic dome and loss of fat tissue around the hiatus at the esophageal hiatus result in herniation. This would help explain the frequent finding of hiatal hernia in elderly people.

Weintraub[2] states that herniae through the esophageal hiatus are by far the most common. Harrington found 80 per cent at the esophageal hiatus among 430 patients undergoing surgery, including 12 with congenital short esophagus and 17 with history of trauma, 9 at the foramen of Bochdolek and 8 at the foramen of Morgagni. The herniations of the remaining 70 cases were due to congenital defects of the diaphragm, direct and indirect injuries or necrosis resulting from infection[2].

Symptomatology

Recent studies have shown that diaphragmatic hernia is a common condition and that it has often been overlooked in the past because of misinterpretation of the symptoms as being on a functional basis. The distress at first may be in the mid-line of the epigastrium, below or behind the xiphoid process. It may be interpreted by the patient as being of ulcer type, and there may be dysphagia to indicate the high location of the disorder[9]. Pain frequently occurs in a reclining or recumbent position, being relieved by standing erect or sitting up. "Anginal pain" is frequently simulated, any time of the day or night, but more frequently after meals. The embryonic origin of both the heart and the central portion of the diaphragm in the cervical region accounts for the similarity of symptoms. Pain of the hiatus hernia probably is mediated

over the viscero-afferent fibres from the diaphragm contained in the phrenic and the middle and lower dorsal spinal nerves. Overdistention of the lower end of the esophagus or the herniated portion of the stomach, with or without associated esophagitis or gastritis, may produce pain similar in distribution to that of angina pectoris, except that component corresponding to the first thoracic or ulnar distribution[10].

Bleeding may occur, resulting in severe iron deficiency anemias. This is usually due to congestion in mucous membranes and venous enlargement in the walls of the herniated portion of the stomach. Overnight retention of acid gastric secretion in the pouch undoubtedly plays a role as well. Ulcers in the herniated pouch have also been reported. It is suggested that in patients, especially women past middle age with an iron deficiency anemia but without a history of bleeding, without localizing symptoms and significant physical changes, hiatus hernia should be ruled out before other diagnoses are entertained[11].

There may be pain and a feeling of soreness in swallowing with dysphagia, regurgitation, and vomiting of food and acid material. These symptoms are secondary to "reflex esophagitis" and benign stenosis. Benedict and Gillespie[8] emphasize Allison's demonstration of the importance of hiatus hernia in the production of ulceration of the esophagus and subsequent stenosis. He proposed this theory in 1946[12] and outlined the course of the disease as follows:

Regurgitation of gastric juice—inflammation of esophagus—ulceration—fibrosis—stricture formation.

Differential Diagnosis

Gallbladder disease, coronary artery disease, peptic ulceration and carcinoma of the gastrointestinal tract all mimic hiatal hernia. Electrocardiographic and gastrointestinal studies should be done as soon as possible in acute cases. Severe vomiting attacks are a risk in patients who have a fixed hiatus hernia.

Diagnosis

An important feature is for the internist and gastroenterologist to inform the radiologist that he suspects hiatal hernia, therefore assuring the use of radiological studies in the Trendelenburg position, with the patient prone or supine. O'Connor and Ritvo[13] at the Boston City Hospital appreciate the fact that hiatus hernia can be diagnosed on the plain film, without the use of the barium meal. They believe recognition of this could be particularly helpful in view of the widespread use of chest roentgenograms in mass surveys and in routine study of patients admitted to hospitals.

As mentioned earlier in this paper, there is no doubt that the phrenic ampulla is often incorrectly diagnosed as a hiatus hernia[2]. A small pouch imme-

diately above the diaphragm may represent ballooned esophagus or a small segment of herniated stomach. The folds in the pouch at times are unmistakably gastric folds. Frequently, however, the identification of the type of mucosa is impossible. Stretched gastric mucosa may look like esophageal mucosa, and bunched up esophageal folds may simulate tortuous gastric folds[14]. Allison and Johnstone[15] feel that a criterion more important than that provided by the mucosal pattern, however, is the competence of the cardia to prevent gastric reflux. Gary and Schatzki feel that the most reliable roentgenologic sign in the diagnosis of hiatus hernia is the demonstration of a sphincter at the upper end of a questionable pouch.

Treatment

Symptomatic hiatal herniae are medical problems until proved otherwise[16]. The basis of treatment of these uncomplicated cases in our clinic is "full peptic ulcer regime", including a bland diet, antisecretory and antispasmodic drugs, and antacids. Weight reduction is most important in the obese. Sleeping with the head of the bed elevated 6 inches has been of value in preventing nocturnal reflux of gastric secretions into the esophagus. Liquid antacids at bedtime promote nocturnal comfort. In most of our cases we feel the judicious use of psychotherapy and reassurance with full explanation of the genesis of the symptomatology have been of help. When tension was relieved, symptoms abated somewhat. Surgery, we believe, is indicated for recurrent severe pain and vomiting, and serious complications such as bleeding and recurrence of esophagitis, particularly ulcers associated with stricture. After having been on a medical regime, once a second attack of esophagitis has occurred spontaneously, surgical repair of the hernia appears indicated, provided that the patient suffers pain or dysphagia and esophageal damage can be demonstrated radiologically[17]. Interruption of the left phrenic nerve can be done prior to abdominal repair of the hernia, as it relaxes the diaphragm. "Gas on the stomach", heartburn and belching are not reason enough for surgical intervention. In selected cases, esophageal bouginage alone with dilatation of the stricture suffices to bring relief.

Case Reports

Case 1:—Demonstrates symptomatic hiatal hernia mimicking coronary occlusion in a patient with proven coronary artery disease.

A 50-year old white female housewife, a very tense thin person, with history of posterior myocardial infarction 6 months prior to being seen in the emergency room for very severe precordial discomfort, sudden in onset, radiating to the left shoulder and scapular area. Electrocardiogram in the emergency room was not remarkable. She was placed on conservative symptomatic therapy and observed. Repeat electrocardiogram the next morning again was not remarkable. Gallbladder study was normal. Upper gastrointestinal series roentgenograms

revealed hiatal hernia. On "ulcer regimen", raising head of bed, and reassurance patient has not had any further symptoms.

Case 2:—This illustrates hematemesis and epigastric discomfort in a patient with hiatal hernia, bleeding being moderately severe on one occasion. Upper gastrointestinal roentgenograms did not reveal duodenal or gastric ulceration.

A 43-year old obese white male pharmacist, an extremely tense personality, had a history of hematemesis on two occasions in the past, ascribed to "probable stomach ulcer". Present complaint of "dull cramping" in xiphoid area after eating was investigated by roentgenographic study revealing a large hiatal

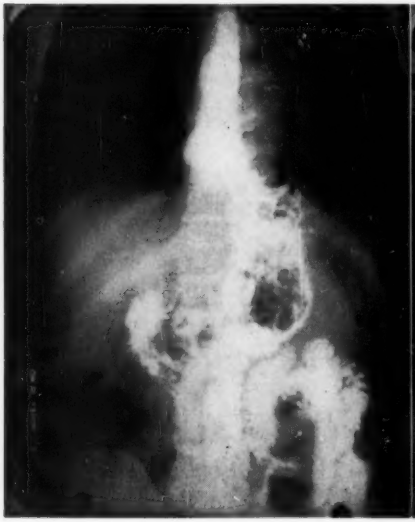

Fig. 1

Fig. 2

hernia (Fig. 1). Surgical repair was carried out, after weight reduction and ulcer regimen failed.

Case 3:—Demonstrates symptoms probably due to hiatal hernia, although initially the gallbladder was suspected.

A 49-year old thin white female housewife with right upper quadrant discomfort, nausea and severe vomiting for several months. This patient was extremely nervous, having had "migraine headaches for years". Cholecystogram interpreted as cholelithiasis. Removal of gallbladder confirmed this diagnosis, but symptoms persisted. Repeat roentgenogram of the upper gastrointestinal tract demonstrated hiatal hernia. Repair of this was carried out, with a subsidence of abdominal symptoms and lessening of the tenseness.

Case 4:–That of pernicious vomiting due to a large hiatal hernia.

A 53-year old white male telephone company employee, average build, with complaint of vomiting after heavy meals, especially if lying down. He had been taking "hormone shots" for nervous tension. Gastrointestinal series study in 1952 had been negative, but because of "night pain" he was treated as an ulcer with fair alleviation of symptoms. Trendelenburg pictures revealed a large hiatal hernia and an old duodenal deformity. A medical regime failed to give relief, hence surgical repair of the hernia was done. Patient became asymptomatic, with considerable improvement in the tension picture.

Fig. 3

Fig. 4

Case 5:–Shows that reassurance and conservative regimen can alleviate symptoms.

A 66-year old white female housewife of average weight, whose only complaint was mild precordial discomfort after eating. Because of "two heart attacks in the family" she wanted a complete examination including electrocardiographic study. The latter was normal. Upper gastrointestinal tract study revealed a large hiatal hernia (Fig. 2). The use of antacids, raising the head of the bed and reassurance has alleviated the complaints.

Case 6:–Demonstrates rapid response to "full ulcer" regimen.

A 46-year old obese white female housewife with only complaint being "burning sensation" in esophagus, not particularly related to meals, and some-

what relieved by milk. Upper gastrointestinal tract roentgenograms revealed a small hiatal hernia with esophagitis and spasm (Fig. 3). On a regime consisting of elevation of head of bed, ulcer diet, antacids and anticholinergics she responded rapidly.

Case 7:—Emphasizes the absolute necessity of surgical intervention in some cases, even though they are "poor risks".

A 70-year old white female with a complaint of high epigastric fullness and pressure coming 30 minutes after meals. Occasionally she experienced precordial distress. Induced emesis relieved the distress promptly. This patient was operated, revealing a large esophagogastric hiatal hernia (Fig. 4). Convalescence was stormy, being complicated by a severe pseudomembraneous enterocolitis.

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CRICOPHARYNGEAL ACHALASIA*

Report of Three Cases

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Introduction

Cricopharyngeal achalasia, as described by Asherson in 1950, is characterized by 1. neurogenic imbalance with dilatation of the hypopharynx, and 2. spasm of the cricopharyngeal muscle. Literature on the subject is limited to Asherson's report. No therapy has been suggested.

Stages of Deglutition

Motion picture radiography has clarified our knowledge of the mechanism of the three stages of deglution.

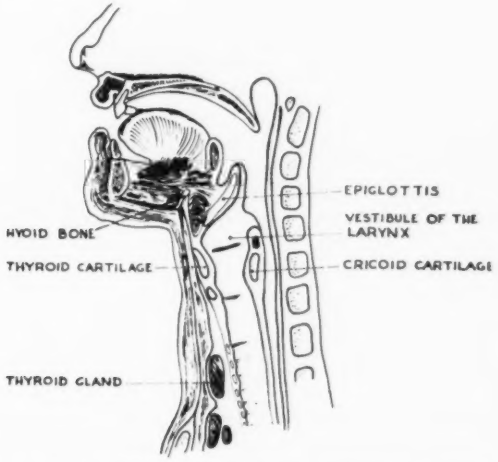

Fig. 1–Saggital section of the larynx, pharynx and esophagus.

First stage – Voluntary contraction of the tongue muscles forcing the bolus from the oropharynx.

Second stage – Elevation of the larynx with involuntary constriction of the pharynx forcing the bolus into the esophagus.

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Third stage – Involuntary contraction of the circular fibers of the esophagus propelling the bolus into the stomach.

Cricopharyngeal dysphagia is primarily a disorder of the second stage of swallowing.

Function and Innervation of the Cricopharyngeal Sphincter

The cricopharyngeal sphincter (lowest fibers of the inferior constrictor of the pharynx) arises from the lateral aspect of the cricoid cartilage to encircle the esophageal orifice. This sphincter, innervated by the inferior laryngeal nerve, remains in tonic contraction and relaxes only when food passes down the pharynx to the esophagus. With the cricopharyngeus relaxed, the cricothyroid muscle, innervated by the superior laryngeal nerve, draws the cricoid cartilage to the thyroid cartilage and thus narrows the larynx during swallowing. The inferior

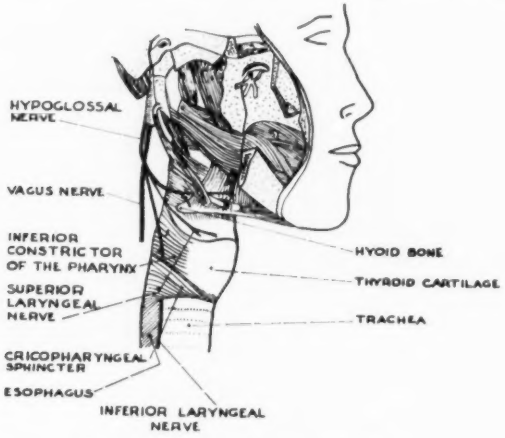

Fig. 2–Lateral aspect of the pharynx.

constrictor of the pharynx, innervated by the posterior branch of the inferior laryngeal nerve, courses posterosuperiorly and elevates the larynx during its contraction. As the laryngeal aperture closes and the larynx rises, the esophagus opens in a funnel-like manner, due to its anterior attachment to the cartilages of Santorini.

Effect of Superior and Inferior Nerve Injury on Swallowing

The main interest of this presentation is in cricopharyngeal achalasia subsequent to inferior laryngeal nerve injury and disease. This interest was aroused from observing the dysphagia in patients with bilateral inferior laryngeal palsy after thyroidectomy.

Case Reports

Case 1:—L. P., a 33-year old white female weighing 78 pounds, noticed a choking sensation on swallowing at the age of 12. Initially, raw apples, popcorn and nuts were the chief offenders. She noticed that if a particle of food touched a particular spot in her throat she would experience an electric shock that would last from three to five minutes. She was esophagoscoped in April, 1950, and narrowing and atrophy of the mucosa at the esophageal orifice was noted. A thin membrane running along the left lateral wall of the esophageal orifice was purposely ruptured during esophagoscopy. In December, 1952, esophagoscopy was negative but an esophagram revealed deviation of the flow of the bolus to the left in the mid-cervical region. The left pyriform sinus retained barium after repeated swallowing and the patient had difficulty in initiating deglutition. The interruption of normal peristalic waves was believed to be on a neurogenic basis. On December 13, 1953, the right superior laryngeal nerve was sectioned and the patient experienced complete relief of her right superior laryngeal

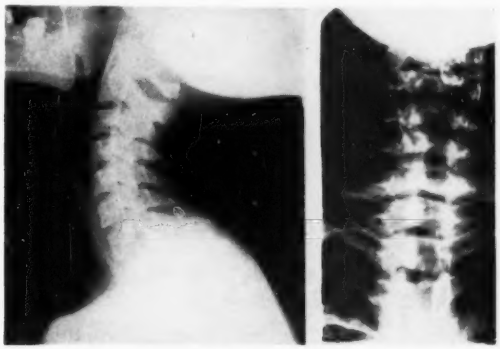

Fig. 3

neuralgia. The intermittent sensation of an electric shock in the right hypopharynx was no longer noted. She has shown no improvement in swallowing, however, is unable to swallow large particles or swallow lying down. She must keep her neck extended prior to elevation of the larynx in the second stage of swallowing. Her weight is still 78 pounds.

Case 2:—M. L., a 36-year old white female, weighed 193 pounds at the time of a thyroidectomy, April 22, 1954. Immediately postoperatively, she showed signs of bilateral inferior laryngeal palsy with difficulty in phonation and respiration. In addition, she complained of difficulty in initiating deglutition, being forced to concentrate on swallowing, inability to swallow lying down, and inability to drink out of a fountain. She noticed that Coca-Cola and candy were particular offenders. On November 11, 1954, a modified right King operation was performed with excellent results as to phonation and respiration. Dysphagia

has been accentuated since the arytenoidectomy and an esophagram taken March 11, 1955, showed difficulty in initiating swallowing but no dilatation of the pharynx. The patient is forced to extend her neck and concentrate on swallowing to prevent gagging and coughing. She feels as though something is

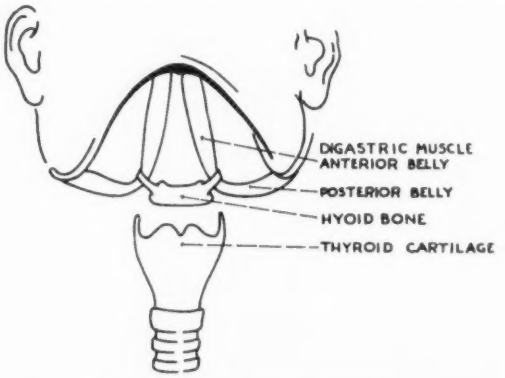

Fig. 4—Digastric muscle anatomy.

pressing on her throat and she must swallow around it. She has lost 44 pounds in the past year and presently weighs 149 pounds.

Case 3:—Mrs. J. W., a 36-year old white female weighed 139 pounds at the time of her thyroidectomy in August, 1951. Subsequent to thyroidectomy signs

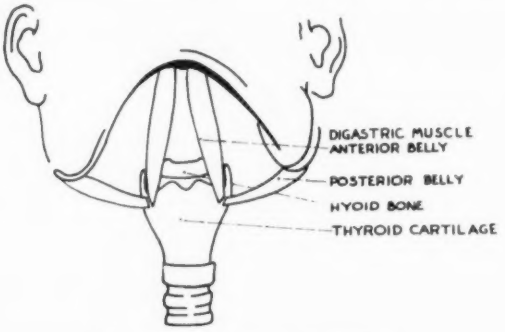

Fig. 5—Digastric transplant operation.

of bilateral recurrent laryngeal palsy were noted. The patient had difficulty breathing, talking and swallowing. In June, 1952, a right King operation was done, for relief of respiration and phonation, with excellent results. The dysphagia noted prior to the King operation was accentuated thereafter and esophagram

showed the bolus of the barium was deviated to the right at the level of the fifth cervical vertebra and barium was retained in the right pyriform sinus. In May, 1954, the patient was esophagoscoped and a constrictive band of scar tissue was noticed in the right pyriform sinus and arytenoid region. This was interpreted as a residual of the right King operation. Dilatation initially produced relief of the sensation of pressure in the right side of her neck, but no improvement in swallowing. The patient experienced difficulty in elevation of the larynx to initiate swallowing, was forced to concentrate on swallowing and was unable to swallow when recumbent. She hyperextended her neck prior to elevation of the larynx in the second stage of swallowing. On February 14, 1955, the anterior and posterior bellies of both digastric muscles were transplanted to the thyroid cartilage in an effort to improve her deglutition. She has experienced complete relief of symptoms, no longer concentrates on swallowing, and is able to swallow in the recumbent position. Re-ray of her esophagus shows no disturbance in deglutition nor hold-up of barium in the pyriform sinus.

Comment

The inferior laryngeal nerves affect the vital functions of respiration, phonation and deglutition. The dramatic symptoms of bilateral inferior laryngeal palsy are dyspnea and dysphonia; dysphagia is a secondary but equally vital consideration. Section of the inferior laryngeal nerves results in paralysis of the inferior constrictors of the pharynx. The patient experiences difficulty in elevation of the larynx to initiate swallowing. X-ray studies are pathognomonic, showing ballooning and apparent lengthening of the hypopharynx retention of the bolus in the valleculae and the pyriform fossa. Lateralization of the vocal cord to relieve the dyspnea (King operation) seems to accentuate the dysphagia, possibly by restricting motion of the cartilages of Santorini.

Clinical Picture

The patient's complaints are characteristic and include concentration on swallowing, difficulty in raising the larynx to initiate the swallowing reflex, hyperextension of the neck during swallowing and inability to swallow when recumbent. This syndrome has been reported as a disease without treatment.

Digastric Transplant

In reviewing the literature, it was noted that Naffziger devised an operation to improve swallowing in one patient with multiple unilateral cranial nerve palsy (ninth, tenth, eleventh and twelfth nerves). This procedure consisted in transplanting the carotid sheath to form a fascial sling about the hypopharynx and attaching the posterior belly of one digastric muscle to the thyroid cartilage. This plan of digastric muscle transplant seems to offer some hope for these desperate people and in one case of this series, the anterior and posterior bellies

of both digastric muscles were transplanted to the thyroid cartilage in an effort to facilitate laryngeal elevation. In this one case the patient has experienced complete subjective and objective relief.

Conclusion

Three cases of cricopharyngeal achalasia have been reported. The relationship of inferior laryngeal palsy to the production of this syndrome has been noted in each of these three cases. In one case, the anterior and posterior bellies of both digastric muscles were attached to the thyroid cartilage and the patient experienced subjective and objective relief.

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FUNCTIONAL CAUSES OF DYSPHAGIA*

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During the last 20 years it has gradually become recognized that the esophagus along with other organs in the body is often the site of reactions to emotional factors. This fact is frequently not appreciated by clinicians in the interpretation of symptoms referable to the chest and has likewise been neglected, to a great extent, in present day medical teaching.

There are three main functional causes of dysphagia: 1. Globus hystericus; 2. Diffuse spasm of the esophagus and 3. Cardiospasm. To this might possibly be added a new entity recently described by Ingelfinger[1] and designated as a contractile ring in the lower esophagus. Ingelfinger described six cases whose symptoms came on following ingestion of certain types of food or when solids were swallowed hastily without mastication. I have not personally seen, or at least recognized a case of this disorder and until we know more about it, judgment should be reserved as to its proper classification.

Globus Hystericus

We are all familiar with this symptom. It is frequently described by patients as "a lump in the throat which I can't swallow". Globus is generally felt to be of emotional origin and coincides with stress and strain factors in the life situation of the individual. The precipitating factor can usually be elicited without difficulty if it is sought for. It should be emphasized that globus can occur alone or in combination with other symptoms. In the latter case, it should at least direct one's attention toward the functional and emotional aspects of the problem. Treatment consists of reassurance as to the absence of organic disease, mild sedation and psychotherapy.

The patient should be encouraged to discuss the factors which precipitated the illness. Ventilation of itself is often extremely helpful therapeutically and in addition every effort should be directed toward helping in the solution of the particular problem with which the patient is confronted at the time.

Diffuse Spasm of the Esophagus

In clinical practice all variations of this disturbance are seen from those which are mild and readily treated to the most severe. Fortunately, the latter group is comparatively rare because they are extremely difficult therapeutic

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problems. The milder cases frequently complain of pain or tightness at any level of the chest along the course of the esophagus. This may or may not be accompanied by dysphagia, which is usually mild and incomplete. Symptoms are generally noted to coincide with emotional crises in the life of the individual and are often intermittent. Diagnosis is made from the history, complete physical examination and laboratory studies, including barium roentgenograms of the esophagus. The latter may be negative if the patient is at ease, or may show mild intermittent esophageal spasm. At times, esophagoscopy may be necessary to settle the diagnosis. Treatment is essentially the same as that outlined in the globus cases above.

In the more severe cases of diffuse spasm of the esophagus, the symptoms are apt to be more persistent and dysphagia more prominent. Pain referred to the mid-esophageal region is often present. Food may reach the middle or lower

TABLE I

SYNONYMS FOR CARDIOSPASM

1. Spasm
2. Simple ectasia
3. Atony and idiopathic dilatation of the esophagus
4. Megaesophagus
5. Hiatal esophagismus
6. Functional hiatal stenosis
7. Phrenospasm
8. Preventriculosis
9. Achalasia of the cardia

third of the esophagus, stop, and then be regurgitated. This group is apt to be more disturbed emotionally, perhaps accounting for the more persistent character of symptoms. The latter are, however, noted to fluctuate or be absent for varying periods, often in relation to the nervous state of the individual, and this should give a clue to the nonorganic nature of the disturbance. Barium swallow will usually confirm the diagnosis and reveal rather severe spasm involving the lower one-third or one-half of the esophagus, accompanied at times by secondary dilatation of the esophagus. The treatment of this group by esophageal dilation and surgery has been, in general, unsatisfactory. Consequently, every effort should be directed towards the correction of the emotional and nervous factors which have precipitated the illness. Some of these cases may be secondary to such organic lesions as esophageal hiatal hernia or esophagitis. In that case, treatment should be directed toward the primary disturbance.

Cardiospasm

Cardiospasm is a most fascinating condition and one whose etiology is still unresolved. The many synonyms which have been used to describe it have usually been chosen in an effort to portray what various investigators have felt to be the most descriptive term (Table I).

Some of the etiologic theories which have been advanced are listed in Table II.

It should be pointed out that in some patients with cardiospasm, the disturbance is apparently of reflex origin, secondary to such intraabdominal conditions as peptic ulcer, gallbladder disease, etc. Four of our patients under treatment for duodenal ulcer complained of dysphagia and pain beneath the xyphoid when Banthine was added to the program. Ingelfinger has recently

TABLE II

Theories of Etiology

1. Primary atony of esophagus (Finkelstein)
2. Congenital factors (von Hacker)
3. "Diaphragmatic pinchcock" (Jackson)
4. Abnormalities in "liver tunnel" (Mosher)
5. Spasm (Knight)
6. Failure of relaxation: "achalasia" (Hurst)
7. Degeneration of Auerbach's plexus (Rake)
8. Nutritional deficiency states (Etzel)
9. Autonomic and reflex factors
10. Psychogenic factors (Weiss; Faulkner; McMahon, et al.)

demonstrated the retention of swallowed barium in the normal human esophagus for more than ten minutes after the intravenous injection of Banthine, information which points the way to our understanding of the pathogenesis of cardiospasm.

I should, however, like to exclude this group and summarize the recent work concerning the role of psychogenic factors in the etiology of cardiospasm. One of the earliest studies from the psychosomatic standpoint was that of Weiss[2] who reported nine cases, presenting symptoms arising coincidentally with an emotional conflict, in many instances during puberty, and whose early life gave evidence of personality difficulties. It was his opinion that cardiospasm is a psychosomatic disorder, an organ neurosis corresponding to a form of conversion hysteria deeply rooted in the unconscious mental life of the individual. Faulkner[3-6] reported extensively on the role of psychologic factors in the function

of the esophagus and presented very interesting observations on the production of esophageal spasm in patients during esophagoscopy. The spasm he witnessed could be increased, with demonstrable narrowing or complete closure of the lumen, by suggestions which produced destructive emotions such as grief, anger, anxiety, apprehension, fear, and spiritual imprisonment. The opposite response was obtained during the experience of such emotions as happiness, elation, enthusiasm, contentment and security. He concluded that disturbing emotional factors and influences are underlying factors in the production of cardiospasm and that in addition to esophageal treatment, the patient's environment and mental outlook should be improved and emotional re-education instituted. Wolf and Almy[7] have recently presented some most interesting data pertaining to emotional factors in cardiospasm. They studied a group of patients with the condition, making a thorough inquiry into the life situation, background and

TABLE III

PERSONALITY PATTERNS IN CARDIOSPASM

1. Perfectionistic, neat, orderly and with meticulous makeup.
2. Energetic but with surprising lack of aggressiveness.
3. Emotionally dependent.
4. Unusually submissive.
5. Exceptionally sensitive; easily offended.
6. Harbor resentment.
7. Shy, bashful, with strong feeling of inadequacy.
8. Hard to approach.
9. Suppress true feelings.
10. Like to be well thought of; avoid arguments.

personality of the individual involved. They then timed fluoroscopically the passage of barium from the throat into the stomach when the individual was secure, relaxed and at ease, and found it to be within normal limits of eight to twelve seconds. Known distressing life situations or emotional factors in the life of the individual were then introduced into the conversation, following which the cardia was observed to tighten rapidly and the swallowing time was prolonged up to 30 minutes. When the individual was again made to feel more secure and his mind taken off his problems by changing the conversation, the cardia would open and barium passed through normally. This is striking evidence of the role of the emotions in cardiospasm, as demonstrated in the modern experimental laboratory.

In 1951, Braceland, Moersch and I[8] published the results of a study of 25 cases of cardiospasm, all of the classical type with dilated esophagus. We were able to define a common personality pattern (Table III).

In our group, as a whole, the onset of dysphagic symptoms was generally found to follow episodes of psychic trauma. It was noted in 19 cases that symptoms were always worse when the patient was nervous, upset or under emotional strain. In four other patients the symptoms had remained stationary since the onset, as had the precipitating factors or situation. Recurrence of symptoms after treatment could be linked as readily to psychic trauma as was the onset of the illness. The frequent rapid fluctuation of symptoms clinically, in most patients, further bears out the work of Almy and Wolf. For instance, an individual may be eating in a restaurant having little or no difficulty, then become suddenly upset and immediately develop dysphagia. Later, in the quiet of his own home, when he is no longer upset, the food may again go down perfectly or with relatively less trouble.

Precipitating factors noted at the time of onset of symptoms included resentment or anger, usually suppressed; economic loss or insecurity—often catastrophic; death of a parent—on whom the patient was abnormally dependent; feeling of rejection, usually by a member of the family; fears of death, insanity or failure; frustration, and the menopause.

Other interesting data from this study is listed in Table IV.

TABLE IV

DATA FROM PSYCHOSOMATIC STUDY, 25 CASES

1. Family history of disease	3
2. Neurotic traits in family background varying from alcoholism to psychosis	17
3. Neurotic traits in childhood	22
4. Other neurotic traits during adult period	23
5. Concomitant depression	18

Study of the family backgrounds in the group revealed definite evidence of neurotic traits varying from alcoholism to psychosis. In three additional cases, evidence for the same was classified as suggestive; for example, extreme nervousness or migraine in a parent. Neurotic traits in childhood included enuresis, nailbiting, temper tantrums, phobias, etc. Evidently, these traits did not end in childhood, for 23 patients (that is, all but one, if the single child studied is excluded) manifested other neurotic traits during the adult period. These included depression, frigidity, inferiority complexes, anxiety states, inordinate masculine drives, inability to accept authority, abnormal dependence on and attachment to a parent, abnormal grief, poor psychosexual development, migraine and duodenal ulcer. Interestingly enough, at the time of our study, 18 of the 25 patients were found to be suffering from varying degrees of depression. In at least two cases, the depression was of sufficient depth to cause consideration of hospitalization for electro shock therapy. The response to superficial ventilation

of the patient's emotional problems and to supportive therapy in the form of reassurance, encouragement and discussion of problems, however, warranted a postponement of this measure. The definite impression was gained that the depression was more often than not a reaction to the basic emotional problems that had precipitated the condition itself rather than a secondary reaction to the cardiospasm.

Some of the commonly accepted methods of treatment are as follows: 1. Drugs; 2. dilatation; 3. surgery; 4. oral Procaine and 5. psychotherapy.

Drugs:—Most authorities are in agreement as to the ineffectiveness of pharmacologic methods especially in those cases which have progressed to secondary dilatation of the esophagus.

Dilatation:—Dr. Herman Moersch[9] has pointed out that it is impossible to set down any hard and fast rule as to the most satisfactory method of treating cardiospasm in any given case as there are so many variable factors to be considered. By and large in proper hands, dilatation has been shown to be effective in the largest percentage of cases. The most extensive experience reported has been that of Olsen et al[10] at the Mayo Clinic and their conclusion was that dilatation is the treatment of choice for most patients. Relief of dysphagia after two courses of treatment was obtained in 75 per cent of 142 cases for a period of from 4 to 16 years. If no relief was obtained by the second course of treatment, satisfactory results were not likely to be obtained. About 20 per cent of patients cannot be permanently relieved by dilatation. Surgery was reserved for those cases which failed to respond to two or three courses of dilatation and should be carried out, when necessary, before marked changes in the esophageal wall have taken place.

Surgery:—There has been no general agreement as to the proper type of surgery, though in general, the Heller procedure has been favored. In many patients the problem of peptic esophagitis due to regurgitation of acid gastric juice, has been a formidable one postoperatively and in order to circumvent this, Wangensteen[11] has introduced an esophageal antral anastomosis with excision of the lower esophagus and the entire acid secreting area of the stomach with simultaneous pylorotomy. To the best of my knowledge, this procedure has not gained acceptance generally.

Oral Procaine:—Balfour and Wharton[12] reported gratifying results from the use of oral procaine hydrochloride in the treatment of a small group of cases. I know of no large series of cases in the literature treated by this method alone and properly controlled. I have had a small personal experience with this method of treatment and would consider it to be of most value as an adjunct to treatment of esophagitis with or without accompanying esophageal spasm.

Psychotherapy:—The chief aim of the study reported by Braceland, Moersch and myself was to assay the role of emotional factors in the etiology of cardio-

spasm and to define a personality pattern if possible. No psychotherapy was intended as such. We were impressed, however, by the large number of patients who suffered from concomitant depression, as well as the not infrequent improvement in their affective symptoms following superficial ventilation. Likewise, we were interested in the experience of Walsh[13] who had the opportunity to treat a patient by psychotherapy alone. A young woman was under treatment for severe cardiospasm with marked esophageal dilatation. Even with the aid of a previously swallowed thread, the dilator could not be passed through the cardia despite repeated attempts. Because of marked weight loss and complete inability to swallow, surgery was recommended but refused. Neuropsychiatric consultation was requested and Walsh immediately recognized emotional problems of a serious nature. After a few days of no other treatment but psychotherapy, the patient was swallowing without difficulty and within a two-week period had gained over 25 pounds. Follow-up over a year later revealed that she had maintained her weight gain and had relatively little dysphagia in the interim.

The implication from this data is that psychotherapy should be an integral part of the treatment of every patient suffering from cardiospasm. Depending upon the degree of emotional disturbance, this may at times need to be on a formal basis. In most instances, however, this is not necessary and generally speaking, the managing physician, by being aware of the emotional factors involved, can have an additional therapeutic tool at his disposal. The willingness to allow the patient to unburden himself, the provision of a warm sympathetic environment and understanding by all personnel concerned, and brief daily talks have all proven helpful. We have now had the opportunity to follow a small group of cases in which psychotherapy was made a part of the management of the patient and have noted, that in several instances, improvement in swallowing took place before dilatation was undertaken. In two instances, where dilatation was impossible for various reasons, the patient responded to psychotherapy alone.

Summary

1. The three functional causes of dysphagia are globus hystericus, diffuse esophageal spasm and cardiospasm.

2. The bulk of recent evidence would indicate that cardiospasm is a psychosomatic disorder.

3. Psychotherapy is recommended as an integral part of the management along with dilatation.

4. Mild cases may respond to psychotherapy alone.

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CARCINOMA OF THE PANCREAS*

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In 1888 Bard and Pic advanced the concept that malignant lesions of the pancreas and the ampulla of Vater areas are characterized chiefly by painless jaundice. This concept found its way into textbooks and for many years obscured the real clinical picture and prevented the early diagnosis of this disease.

A review of the literature reveals the fact that pain precedes jaundice in approximately 80 per cent of all cases of carcinoma of the pancreas. There are four main types of pain recorded: 1. A steady, dull mid-epigastric pain extending through to the back; 2. A paroxysmal pain beginning in the mid-abdomen and radiating diffusely over the abdomen, chest and back; 3. A cramping pain beginning in the right hypochondrium and radiating to the subscapular region; 4. A sharp, penetrating, severe pain in the left loin and back, which is often relieved by changes in posture. In general, the location of the pain bears a direct relationship to the site of the lesion in the pancreas and to the involvement of the surrounding structures. If the tumor has invaded the entire pancreas, these several types of pain may occur in the same patient. The pain of carcinoma of the pancreas is rarely influenced by the ingestion of food. The pain of early carcinoma may be vague, fleeting, and often not mentioned by the patient unless carefully questioned. Late in the disease, however, the pain may be severe, constant, and the patient may require frequent opiates. The pain is usually worse at night, or on assuming a recumbent posture.

Jaundice occurs in about 75 per cent of cases in some stage of the disease. It is more likely to occur early in carcinoma invading the head of the pancreas, or the ampulla of Vater. Painless jaundice may be the first symptom noted in from 15 to 20 per cent of patients. The jaundice varies in severity according to the degree of duct obstruction. In carcinoma of the tail of the pancreas jaundice may not occur during the entire course of the disease.

Weight loss is the most constant symptom. It may vary from a few pounds to as many as 50 pounds. Loss of weight is due to reduction in food intake, inadequate digestion and absorption, and the excessive metabolic activity of the neoplasm. Anorexia, nausea and vomiting occur in nearly all patients at

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some stage of the disease. Diarrhea is rare, but constipation is a common symptom.

The physical examination may reveal no positive findings in early carcinoma of the pancreas. Jaundice, when present, is due to extension of the growth and obstruction of the common duct, or ampulla. It may be partial or complete. When complete, there is usually persistent pruritus of the skin. When the common duct is obstructed, the gallbladder usually is enlarged and may be palpated. The pancreas being located posteriorily is not palpable unless the tumor is large. The liver may be enlarged if there is metastasis present, or if the ducts are obstructed. In the latter case the hepatomegaly is due to a biliary type of cirrhosis. These patients usually show a pallor of the mucous membranes as the result of secondary anemia. Weight loss is apparent when digestion is impaired.

The x-ray examination is negative in early carcinoma of the pancreas. When the tumor occupies the head of the pancreas, there may be a widening of the duodenal loop. Extension of the tumor to involve the stomach, the duodenum, or the colon may be evident on x-ray as a filling deformity in these viscera. In fact, many patients have shown partial or complete intestinal obstruction. If the tumor involves the body or the tail of the pancreas only, erosion of the spinal column at the level of the 10th, 11th, 12th dorsal, or 1st lumbar segments may be found. Also, a pyelogram may show deformities of the renal structures if the kidneys are involved.

The laboratory examination, like the x-ray, in early carcinoma of the pancreas reveals negative information. When jaundice is present it is usually the obstructive type. The icterus index is elevated and hyperbilirubinemia is found. When the insulin producing cells are destroyed the glucose tolerance curve is elevated and sugar spills over in the urine. Liver function studies yield positive information only in proportion to the extent of liver damage. Metastatic involvement of the liver from any source will yield similar laboratory data. Serum lipase and serum amylase may or may not be elevated. When elevated, it simply denotes disease in the pancreas and is not diagnostic of carcinoma.

The clinical diagnosis of carcinoma of the pancreas in the early stage is impossible. The vagueness of the symptoms and the absence of all clinical findings should arouse suspicion and frequent examination is warranted. We are sure all of us have had the experience of studying a patient who has had vague gastrointestinal symptoms and have found no evidence of disease, only later to have the patient return (or go elsewhere) with full blown evidence of advanced carcinoma of the pancreas and metastasis into surrounding structures.

Primary carcinoma of the liver may present the same type of digestive symptoms. The chief distinguishing features are, enlarged, hard, nodular liver

with pain worse in the right upper quadrant through to the back and right shoulder. Chills and fever are common in carcinoma of the liver.

Carcinoma of the gallbladder occurs most frequently in woman. The symptoms are not very different from those of carcinoma of the liver. If, however, a patient has suffered with gallbladder disease over a long period followed by a recession of symptoms, then has recurring severe symptoms, carcinoma of the gallbladder should be suspected. It is variously estimated that stones are present in the gallbladder in from 65 to nearly 100 per cent of cases of gallbladder cancer. Pain, fullness, and a burning sensation over the right upper quadrant and the palpation of a hard, fixed mass in the region of the gallbladder is further evidence of carcinoma of the gallbladder.

Carcinoma of the extrahepatic ducts and ampulla of Vater is less common than carcinoma of the pancreas or gallbladder. The symptoms and signs vary little from those of carcinoma in the head of the pancreas. The progress of the disease is rapid. Right upper quadrant pain, nausea, vomiting, chills and fever are frequent symptoms. Early duct obstruction and jaundice is the rule.

In cirrhosis of the liver the symptoms are of much longer duration. Jaundice is late in appearing and pain is rarely present. Edema of the lower extremities, ascites, the appearance of enlarged veins on the chest and upper abdomen, hematemesis and other signs favor cirrhosis.

In spite of all known diagnostic studies, carcinoma of the pancreas is still difficult to diagnose. Exploration by surgical means is often necessary to make the diagnosis. We must bear in mind the vague pains in the upper abdomen through to the back, moderate indigestion, and rapid loss of weight. These are the most constant clinical findings in carcinoma of the pancreas.

From 1933 to 1950, 85 patients were diagnosed as having carcinoma of the pancreas at Sanders Clinic. Twenty-two were diagnosed clinically only; were all in advanced stage and were considered hopelessly inoperable. None of them lived longer than four months.

Three patients at operation were found to have carcinoma of the stomach and pancreas. We were unable to determine if the primary lesion originated within the stomach and perforated onto the pancreas, or began in the pancreas and perforated into the wall of the stomach.

Sixty patients were operated upon and were proven to have primary carcinoma of the pancreas. There were 38 males (61 per cent) and 22 females (39 per cent). The youngest was 40 years old, the oldest was 80 years. The average was 64 years.

Symptomatically, 42 (70 per cent) complained of moderately severe pain. Eighteen (30 per cent) were painless. Forty-seven (71 per cent) were jaun-

diced, and 13 (29 per cent) had no evidence of jaundice. All of them had indigestion, nausea, or vomiting.

The average duration of symptoms preoperatively was four months. The longest was 18 months, the shortest two weeks.

They all had lost from 10 to 45 pounds in weight. The general average was 20 pounds.

X-ray examination was not done on 20. All of these were jaundiced and had a palpable mass in the upper abdomen. Forty patients had gastrointestinal x-rays done. There was positive findings in 11 (28 per cent), and negative findings in 29 (72 per cent). The positive results were, deformity of the duodenum, stomach, or colon as the result of direct extension of the tumor to one of those viscera. A large duodenal loop was seen in five patients.

The tumor was located in the head of the pancreas in 30 patients (50 per cent), the body of the pancreas in 27 (45 per cent), and the tail in only 3 (5 per cent). In the three patients with carcinoma of the tail of the pancreas, none were jaundiced and the pain was located in the back and left loin.

At operation 28 (46 per cent) were found to be hopelessly inoperable and biopsy alone was done. Thirty-two patients (54 per cent) had anastomosis of the biliary tract to the duodenum or jejunum. None were considered favorable for radical resection.

The length of survival was as follows: Less than 1 month—4. From 1 month to 12 months—50. Twelve to 24 months—5. Only 1 patient lived for 31 months.

It is interesting to note that one patient in our series was operated upon and found to have a very large, hard pancreas, a large liver, and was deeply jaundiced. Biopsy from the pancreas was reported as carcinoma. Nothing further was done. Her symptoms gradually disappeared and she was fairly well for eight years, when she returned deeply jaundiced again and had symptoms of intestinal obstruction. At operation it was found she had an extensive carcinoma of the pancreas with metastasis in the liver, stomach and small bowel producing intestinal obstruction. We are unable to explain why she lived eight years without any treatment. We believe, however, she must have had a pancreatitis at the first operation. Unfortunately, the pathologist had misplaced the specimen removed at the first operation, and we were unable to review it in the light of the findings at the last operation.

In 1935, Whipple demonstrated a radical operative procedure for early carcinoma of the head of the pancreas and the ampulla of Vater. The patients selected for this operation necessarily must have carcinoma in the early stage with no demonstrable evidence of metastasis. The operative mortality in the various series reported range from 11 to 50 per cent, the average being 25 per cent.

Follow-up results on the survival of patients who were subjected to the Whipple operation shows that only about 2 per cent survived for five years.

The Whipple operation was done by one of us (R. McB.) on four patients during the last two years with no operative deaths. One of these patients is dead. One is living with no evidence of metastasis for 14 months, the others are living, 16 months and 8 months, but have metastatic disease.

Early diagnosis and the performance of the radical operation of Whipple offers hope of survival for patients with carcinoma of the pancreas, albeit a rather slim one.

The two following cases are examples of the obscurity and difficulties that may attend diagnosis in some cases:

Case 1:—A male, age 52, came to the clinic in March, 1944 complaining of severe pain in his mid-back. He stated that four months previously, while carrying a heavy bundle under his left arm, he stepped off the sidewalk onto the street and was seized with a sharp pain in his back, radiating to the left loin and left upper abdominal quadrant. The pain had continued growing more severe. He was relieved somewhat by lying in bed and flexing the left leg, or sitting with the left knee flexed on the chest. He had taken considerable amount of opiates and barbiturates with little benefit. He had been examined by five different physicians, but no diagnosis had been established. He had no other complaints, except vague digestive symptoms which he attributed to the medicine he was taking for relief of pain.

On entering the examining room he got down on his right knee and pulled the left knee up against his chest. He said that this position gave him some relief. A thorough examination revealed tenderness and muscle spasm in the back at the level of the 10th dorsal to the 2nd lumbar segment. There was no mass felt in the abdomen, but considerable tenderness was noted in the left upper quadrant. Backward motion of the spine and straight leg lifting increased the pain. Otherwise, the examination was negative. There was no weight loss.

Laboratory studies, including urinalysis, complete blood count, Kahn, and NPN, were all normal. X-ray of the spine revealed a slight narrowing of the 10th, 11th, 12th thoracic, and 1st dorsal segments with mild osteoarthritis. The chest, intravenous pyelograms and complete gastrointestinal studies were all entirely negative. He was advised to enter the hospital for spinal fluid studies and myelogram. This was refused. He was not seen again for three months, at which time he was in the amphitheater of the University of Tennessee where he was brought in on a stretcher as a case study for the students. He explained that following our examination he consulted an orthopedist who put a back brace on him, but this made the pain worse. Another physician thought his pain was due to a neurosis and referred him to a psychiatrist. He received two shock treatments which increased the pain. On examination it was noted that

he was deeply jaundiced and emaciated. There was a firm, fixed mass in the left loin, and the liver was enlarged and hard. He died a few days later. Autopsy revealed a large, hard carcinoma of the tail of the pancreas, passing up over and fixed to the spine with involvement of the left kidney, the splenic flexure of the colon, and metastasis into the liver and mesentery.

Case 2:—This patient was a 66-year old retired minister. He was first seen at Sanders Clinic on August 26, 1954. His complaints were, dull pain in the left loin, anorexia, nausea, constipation, weakness, and loss of appetite of three months' duration.

He had been retired by his church and felt greatly depressed, as he realized his life's work was over. He had been under treatment for hypertension for 10 years and recently had considerable dyspnea on exertion, but no chest pain.

He weighed 133 pounds (normal weight 168 pounds); blood pressure was 110 systolic, 80 diastolic. The heart sounds were distant and rhythm was irregular. The lungs were clear, and the abdomen was soft. No masses were felt. The prostate was firm, smooth and slightly enlarged.

The urine showed a trace of albumin and sugar. The leucocyte count was 6,000; hemoglobin was 15 gm.; erythrocyte count was 4,400,000. Kahn test was negative, and blood sugar 112 mg. X-ray of the chest revealed a flattening of the dome of the left diaphragm. The lungs were negative. The thoracic spine showed minimal osteoarthritis. The EKG was normal. The gastrointestinal x-ray was negative. No specific initial diagnosis was made.

He was seen again on November 1, 1954, when he entered the Baptist Hospital seriously ill. He stated he had suffered with severe pain in his back and left side for three days. The pain was present day and night and was not relieved by opiates. He did get some relief by flexing his left knee onto his chest. He had been vomiting all food taken for two days.

Examination revealed that he had lost further weight and appeared acutely ill. Blood pressure was 80 systolic, 50 diastolic. The heart sounds were very faint. The lungs were negative. There was no mass felt in the abdomen, but there was marked tenderness in the left loin. The muscles of his lower back were rigid and the spine was immobile. Straight leg lifting increased the back pain. The position assumed in bed was lying on his right side with the left knee flexed on his chest.

The urine again showed a trace of albumin and sugar. Hemoglobin was 17 gm.; leucocyte count was 18,000 with a normal differential count. The NPN was 90 mg., and serology was negative. X-ray of the spine showed the loss of the normal lordosis and narrowing of the 4th lumbar segment. There was mild generalized hypertrophic arthritis. Intravenous pyelograms showed no excretion of dye in either kidney in one hour.

His condition rapidly became worse, his blood pressure was unobtainable, the abdomen became distended, and there was marked dyspnea. He died on November 5, 1954, four days after admission. He was not jaundiced at any time.

Autopsy revealed carcinoma of the tail of the pancreas with extension to the posterior wall of the stomach and the esophagus, the left adrenal gland, the hilum of the left kidney with occlusion of the left renal vein. There were metastatic lesions in the liver, mesentery, and omentum. Abdominal ascites and pulmonary atelectasis were also present.

Summary

1. Early symptoms of carcinoma of the pancreas are often vague and bizarre. The physical and laboratory examinations are usually negative.

2. There are four types of pain observed in advanced carcinoma of the pancreas: 1. A steady, dull mid-epigastric pain extending through into the back. 2. A paroxysmal pain beginning in the mid-abdomen and radiating diffusely over the abdomen, the anterior chest, and into the back. 3. A cramp-like pain beginning in the right hypochondrium and radiating into the subscapular region. 4. A sharp, severe, penetrating pain in the back and left loin which is often relieved by flexion of the spine and left leg.

3. Eighty-five cases of carcinoma of the pancreas are reported. Thirty-two were far advanced with palpable tumors in the upper abdomen, enlarged hard liver, and jaundice. They were considered hopelessly inoperable. Three cases were explored and found to have carcinoma of the pancreas and stomach, too extensive to determine which was the primary lesion. Sixty cases were operated upon and proved to have carcinoma of the pancreas. Thirty-eight were hopeless and no operative procedure was done. Thirty-two had anastomosis of the biliary tract to the duodenum or jejunum. None were considered favorable for radical resection. Fifty-nine died within two years, and one lived 31 months.

4. Two cases are reported with somewhat unusual symptoms of severe pain in the back and left loin, relieved temporarily by forward flexion of the spine and flexion of the left leg.

5. Finally, patients presenting vague upper abdominal pain with loss of appetite and weight, and with negative laboratory and x-ray studies deserve an abdominal exploration if early diagnosis of carcinoma of the pancreas is to be made and radical resection is to become a curative procedure.

THE IMPORTANCE OF PROPER ACID NEUTRALIZATION IN THE MANAGEMENT OF GASTRIC AND DUODENAL ULCER*

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The varied forms of therapy proposed in articles dealing with the treatment of gastric and duodenal ulcers are valid indications of one unfortunate fact—the etiology of peptic ulcer is still an enigma. To date, no specific therapy has been proposed which is based on the etiology or pathogenesis of the lesion. And, as has been stated[1], critical evaluation of the many "new methods" which have been proposed in the treatment of peptic ulcer leads the physician to the conclusion that the basis of all peptic ulcer therapy is the time-tested procedure of rest, mild sedation, alleviation of psychic stress, appropriate diet, and routine use of an effective antacid. To these measures one may add an antispasmodic or one of the newer anticholinergics when necessary.

Early enthusiasm for simple vagotomy is now quiescent; today the procedure is rarely used. Vagotomy has failed primarily because it has not prevented recurrent ulceration and because subtotal gastric resection has a significantly higher promise of success. "Ulceration may recur while the physiologic effects of vagotomy persist, which bodes ill for the patient who has had primary vagotomy combined with gastroenterostomy."[22] Further, duodenal ulcers should be regarded as a medical disease unless there are extremely good reasons for subjecting the patient to an operation[4]. "Medical vagotomy" through the use of anticholinergic drugs alone also has proven fruitless: "These agents have been disappointing in the long-term management of ulcer, since recurrences are not prevented and the incidence of complications or the need for surgery are not altered significantly by their prolonged administration."[3] Treatment with anticholinergics is not a substitute for more intensive treatment with rest and acid neutralization, but they are often a useful addition to this latter regimen. When administered alone, anticholinergics may even be dangerous because the opportunity for complete healing and the avoidance of complications may thereby be forever lost[23].

Etiology

From the literature, it can be seen that the most generally prevailing opinion is that acid-pepsin activity is of prime importance in the production

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and maintenance of peptic ulcer. The ulceration occurs when the aggressive acid-pepsin factors overwhelm the natural gastric and duodenal defense mechanism which may be locally weakened by circulatory, neurotrophic, endocrine, nutritional and metabolic disturbances[5]. Unfortunately, investigation has as yet also failed to reveal the nature of the abnormalities preceding this breakdown of mucosal resistance to acid and pepsin.

Therapeutic Principles

Although excess hydrochloric acid is only one of the many possible causative factors in peptic ulceration, authorities agree that it *must* be present for such lesions to develop and become chronic[6]. The "acid theory" of ulcer pain has much clinical support. Therefore, therapy must necessarily be directed toward reduction of gastric acidity, protection of the ulcer crater and irritated mucous membrane, and the improvement of the patient's general condition[3,6,7].

Psychotherapy

"The influence of the psyche in the etiology and activity of peptic ulceration is a concept of persuasion to any who have noted and considered it."[8] It has been shown that gastric secretion in man is predominantly under neural control via emotional excitation of the parietal cell, the source of hydrochloric acid. Among the stimuli to sustained gastric hyperfunction, troublesome life situations have been found to be prominent and surprisingly potent, often outweighing the effects of powerful pharmacodynamic agents[9]. Therefore, in practice the psychosomatic aspects of the disease *must* be taken into consideration. Attempts should be made to alleviate psychic stress by whatever practical measures the physician may be able to suggest in regard to the patient's need for reassurance, possible environmental change, solution of personal problems, and other approaches toward enhancement of morale[2]. It must be remembered, however, that psychotherapy alone has accomplished little material benefit for any substantial period of time[1].

Diet

The importance of adhering to dietary restrictions must be emphasized, for as demonstrated since the time of Sippy, proper diet is an essential adjunct to the medical management of peptic ulcer. Protein foods are especially effective in neutralizing excess gastric acidity. Among these, milk and cream have especially high acid buffering properties and are basic foods upon which the soft-bland diet is planned. Meat, poultry, fish and eggs are likewise useful for their acid-neutralizing properties. Fats are well known for their inhibitory effects on the gastric secretion, but their choice should be restricted to those which are highly emulsified, such as are found in whole milk, cream, butter and egg yolk[10].

Careful dietary hygiene protects the stomach and duodenum from chemical, mechanical, and thermal irritation[11].

Anticholinergics

Like atropine, the new cholinergic blocking agents are effective in reducing both secretory and motor activity of the stomach[6,27,28]. These effects may both tend to lessen and abolish pain in patients with active duodenal and gastric ulcers. Their pharmacodynamic effects, however, are not limited to the stomach alone, and most of them produce unwanted effects throughout the parasympathetic nervous system—pupillary dilatation, dryness of the mouth, esophageal spasm, urinary retention, constipation, and fatigability[2]. Therefore, the attempt at "medical" or "chemical vagotomy" through the use of anticholinergics alone has proven unsatisfactory, although *in conjunction* with antacid medication in severe cases, anticholinergics may be highly useful[3,6,27,28].

Antispasmodics

Ganglion-blocking agents such as tetraethylammonium bromide and hexamethonium bromide are effective in lowering gastric acidity by reducing intestinal motility. These substances, however, are too variable in their effects on acid, and too constant in their side-effects to warrant their routine use in peptic ulcer therapy. These drugs should be considered as adjuncts when necessary in the management of both functional and organic gastrointestinal disorders. "As adjuncts they are quite valuable, but as yet fail to be the panaceas first acclaimed."[12]

Miscellaneous

During the last 50 years, practically every endocrine gland has been under investigation both experimentally and clinically for a possible role of hormones in the pathogenesis of peptic ulcer. While a number of experimental and clinical studies appear, however, to suggest a relationship, they fail to demonstrate convincing evidence of such a relationship.

Sex hormones, gastric secretory depressants (enterogastrone, urogastrone) and other "antiulcer" substances (enteroanthelone, uroanthelone) have yet to become established as valuable therapeutic agents in human peptic ulcer[25,26].

Detergents when used in large amounts in the treatment of peptic ulcer, may decrease absorption, partly because of enzymatic inhibition, and partly because of the detergent's irritant effect on the bowel[27].

Therefore, because of the inadequacy of the most recent "advances" in peptic ulcer therapy, the physician must still place the burden of acid neutraliza-

tion and protection of the ulcer and surrounding inflamed area upon effective antacid medication.

Antacid Medication

Thus, the importance of the antacid selected for use in ulcer therapy is clear, since the acid-neutralizing agent is the chief medication prescribed for patients with this disease and is the single most important factor in the therapy of peptic ulcer[13,14]. This fact has spurred efforts to improve presently existing antacids and to produce one which can be considered optimal as regards effectiveness and efficacy.

The early *Sippy powders* are highly effective acid neutralizers. These powders, however, contain absorbable alkaline ions which commonly lead to alkalosis when taken in the large doses necessary to provide relief. Also commonly resulting from the use of Sippy powders are impairment of normal bowel function, stimulation of secondary oversecretion of gastric juice (acid-rebound), and disturbance of the acid-base balance of the body. Thus physicians who continue to prescribe absorbable alkalis in the management of gastric and duodenal ulcers must be on the alert constantly for the development of this toxic clinical picture with the associated findings of hypercalcemia and renal insufficiency[14].

Calcium carbonate has the favorable features of rapid action and high antacid capacity, but when administered as the sole antacid it is unsatisfactory because of its transient effect and its tendency to cause constipation[2,6].

Magnesium trisilicate has no systemic effects, but is slow-acting and limited in capacity to neutralize acid. In the stomach it forms a gel which acts partly by the physical process of adsorption and partly by a slow interaction with hydrochloric acid[2,15].

Aluminum hydroxide, though it does not affect the acid-base balance of the body, is unpalatable, slow-acting, and tends to cause constipation and the formation of concretions in the colon[6,16].

Dissatisfaction with these antacids led to research which brought forth the same antacids in combination, providing a higher degree of therapeutic efficacy with the undesirable effects of one ingredient offset by opposing tendencies of another ingredient. Thus magnesium carbonate was noted to control the constipating effect of calcium carbonate and accordingly the two were combined[7]. This combination, however, has very brief action, is decidedly unpalatable, and does not form a protective colloid film on the inflamed gastric mucosa[17]. Magnesium trisilicate was combined with aluminum hydroxide to counteract the strong tendency of the latter to cause constipation. This combination resulted in an unpalatable antacid with low buffering capacity and slow neutralization of acid.

These "old" combinations have become by far the most widely employed and have sustained their dominant positions in spite of their recognized inadequacies[18].

Recently, a new combination antacid* was termed the closest approach yet made to the theoretical "ideal" antacid[2,13,17,18,19,21]. Its formula is an incorporation of four "standard" antacids—calcium carbonate, magnesium carbonate, aluminum hydroxide, and magnesium trisilicate—plus a vegetable mucin substance† of excellent viscosity, adhesiveness, and spreading qualities, even in highly acid gastric juices[13], which affords protection both to the lesion and to inflamed gastric mucosa. A binding material from cooked oat flour‡ serves to release the antacid ingredients steadily for prolonged acid-buffering activity[13]. Favorable results achieved by others[13,17,18,19] induced the present author to undertake a clinical evaluation of this new antacid.

Clinical Study

Fifty-eight patients suffering from active duodenal or gastric ulcers were selected for evaluation of the antacid properties of Trevidal. Fifty per cent of the patients were ambulatory patients of the Gastrointestinal Clinic of the Jersey City Medical Center and the other 50 per cent were chosen from private practice. All patients had been receiving previously available antacid preparations with varying results. Diagnosis of ulcer was made only after careful examination and verification through x-ray or gastroscopic examination. The initial regimen for all patients consisted of dietary restrictions and two Trevidal tablets every two hours, alternating with a glass of milk every two hours. The group was then divided into two categories: 22 patients remained on Trevidal, two tablets every two hours, plus the bland diet; 36 patients with more or less severe psychic disturbances were given Trevidal, two tablets every two hours, the bland diet, and an anticholinergic every six hours.

The criteria employed for evaluating results were: 1. relief of pain, 2. time necessary for complete symptomatic relief, 3. side-effects, and 4. findings on x-ray and gastroscopic examinations. As improvement was noted, patients were given two tablets every four hours, and finally one tablet four times a day, one hour after meals and at bedtime.

Results

Of the 22 patients in group one (Trevidal plus bland diet), 16 (73 per cent) obtained excellent to good results, with complete symptomatic relief.

*Trevidal®, produced by Organon Inc., Orange, N. J.
†Regonol®, *Cyamopsis tetragonoloba gum.*
‡Egraine®.

Two other patients in this group required the addition of an anticholinergic to the regimen for complete relief.

Of the 36 patients on Trevidal, the bland diet, and an anticholinergic, 28 (77 per cent) became completely asymptomatic after an average of two weeks of treatment.

Side-effects in both groups were minimal. Several complaints of constipation or diarrhea were relieved by a reduction in the dosage of the antacid. Many patients commented on the pleasant "food-like" taste of Trevidal tablets in comparison to the minty, chalky, or sweet flavors of their previous antacid medications.

X-ray examinations two months after initiation of therapy revealed that all gastric ulcers had healed completely. These have remained so to date with no recurrences. The gastric ulcer patients chosen for treatment had lesions of a benign character. All duodenal ulcer patients have remained asymptomatic to date. X-rays have shown the complete healing of many of the duodenal ulcers, and any signs of edema with obstruction have disappeared. Scarred duodenal caps are still evident in many cases.

A particularly outstanding feature of this new antacid is deserving of special mention. Gastroscopic examinations of several patients were made one hour after the administration of two Trevidal tablets. It was observed that a protective viscous gel, resistant to the highly acid gastric juice, had adhered evenly to the ulcer crater and surrounding inflamed mucosal lining. This must be attributed to the action of the vegetable mucin in the Trevidal formula, which, unlike protein gastric mucin, resists digestion by acid-pepsin activity and fosters proper environment for healing of the lesion.

Patients reported immediate relief of "burning searing pain", which relief lasted for several hours after the administration of two tablets.

Comment

When the physician considers the variable results often obtained in antacid therapy of peptic ulcer, and the extensive periods over which the antiulcer regimen must be observed by the patient, the results obtained in this series of patients must be considered outstanding. With few exceptions, the new antacid Trevidal produced immediate yet prolonged relief of pain, adequate protective coating of the ulcer crater and irritated mucous membrane, and virtually no adverse side-effects such as constipation, diarrhea, or acid-rebound. Its palatability and ease of administration assure the physician of complete patient cooperation. When these features are considered against what has been obtained with previously available antacid medication, then Trevidal must occupy the prime position in the physician's armamentarium of antiulcer preparations.

SUMMARY

The specific etiology of peptic ulcer remains an enigma.

With the inadequacy of those preparations originally introduced as "panaceas" in the treatment of peptic ulcer (anticholinergics, antispasmodics), the physician must rely on proven procedures—antacid medication, dietary adjustments, and liberal amounts of reassurance to the patient, using anticholinergics as necessary.

Prior to the introduction of Trevidal, antacids were employed despite their recognized inadequacies: interruption of normal bowel function, low acid-buffering capacity, upset of systemic acid-base balance, unpalatability, and large bulk per dose.

Clinical evaluation of Trevidal in 58 ambulatory patients suffering from active duodenal and gastric ulcers confirmed its value in peptic ulcer therapy. Ulcers healed within three months of the initiation of Trevidal therapy in 46 of the 58 patients (79 per cent). Anticholinergics proved valuable as an adjunct to the antacid in those patients whose conditions were aggravated by psychic difficulties.

Trevidal proved virtually free of side-effects.

Grateful appreciation is expressed to Dr. K. W. Thompson, Medical Director, Organon Inc., Orange, New Jersey, for the generous supplies of Trevidal used in this study.

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THE EFFICACY OF DIHYDROXY ALUMINUM AMINOACETATE IN THE MEDICAL CURE OF PEPTIC ULCERATION

MARION L. RICE, Jr., M.D.*

Kecoughtan, Va.

Rossett and Rice[1], found the relatively new aluminum compound, dihydroxy aluminum aminoacetate, NNR (Alglyn)†, *in vitro*, to be the only aluminum preparation as reactive in the tablet form as the liquid aluminum hydroxide preparation.

Because of the convenience of tablet medication, the present study was undertaken to determine the effectiveness of the tablet form of dihydroxy aluminum aminoacetate in the therapy of peptic ulceration.

Clinical Study

Eighty consecutive cases of roentgenographically proven peptic ulceration were treated by the production of "free achlorhydria" as reported by Rossett et al[2]. The only change in the method was the substitution of dihydroxy aluminum aminoacetate for the mixture of liquid aluminum hydroxide gel and milk of magnesia (4 parts to 1 by volume) used in their report.

This is a representative series of 57 white and 23 colored male ulcer patients ranging in age from 19 to 66 with a mean patient age of 42.55. There were 33 patients with an ulcer history of over 10 years and 61 with a history over 4 years. There were 54 patients with uncomplicated duodenal ulcer (2 postbulbar), 7 with duodenal ulcer plus mild hemorrhage, 2 with duodenal ulcer with obstruction, 1 with duodenal ulcer with obstruction and a gastric ulcer, 3 with uncomplicated prepyloric ulcer, 3 with both an uncomplicated prepyloric ulcer and duodenal ulcer, 1 with prepyloric ulcer with obstruction and mild hemorrhage, 1 with prepyloric ulcer treated following perforation, 1 with gastric ulcer with obstruction, 1 with gastric ulcer (*pars media*) with hemorrhage, 5 with uncomplicated gastric ulcer (*pars media*), and 1 with ulcer in afferent loop of jejunum.

Method

A. *Uncomplicated Peptic Ulcer:*—

1. Bed rest for one week.

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*From the Medical Service, Veterans Administration Hospital, Kecoughtan, Va. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion and policy of the Veterans Administration.

†Dihydroxy aluminum aminoacetate in the form of Alglyn® tablets (0.5 grams) was supplied by the Brayten Pharmaceutical Company, Chattanooga, Tennessee.

2. Convalescent ulcer diet beginning first day of therapy. A Meulengracht type diet was given on the first day only in two cases who had vomited for at least one week prior to admission.
3. Four tablets of dihydroxy aluminum aminoacetate (0.5 gm. each) were chewed well and swallowed with a sip of water, between meals and every two hours at night from 7:00 P.M. to 7:00 A.M., increasing by 0.5 gm. as needed to produce "free achlorhydria".
4. Anticholinergic drug, either l-hyoscyamine sulfate‡ 0.5 mg. q.6.H. or Pamine® 2½ mg. q.6.H., increased cautiously as needed to help produce "free achlorhydria".
5. Neutralization was determined by gastric emptying at 8:45 A.M. before feeding, by placing the patient in the prone Trendelenburg position after passage of a 36 F Ewald stomach tube. If there was a negative reaction to Topfer's reagent (dimethyl-amino-azobenzene), the acidity was determined with a Beckman pH meter. If free HCl was present (positive reaction to Topfer's reagent), medications 3 and 4 above were increased until "free achlorhydria" was achieved.

B. Peptic Ulceration With Mild Hemorrhage:—There were five cases of mild hemorrhage (hemoglobin 8.0-13 gm., average 11.2 gm.) and four cases with moderate hemorrhage (hemoglobin 5.4-7 gm., average 6.4 gm.), requiring 1,000-4,000 c.c. blood. Three were treated according to the "bleeding ceased" regimen of Rossett[2] for 4 days using dihydroxy aluminum aminoacetate tablets. Six were initially treated according to the "bleeding regime" of Rossett[2], using calcium carbonate-magnesium oxide (9:1) mixture and modified Meulengracht diet. After active bleeding had ceased (1-3 days) the "bleeding ceased" regime was ordered. After the first week all were treated as an uncomplicated ulcer.

C. Peptic Ulceration With Obstruction:—The five cases of obstruction were treated according to the obstruction regime of Rossett[2], giving dihydroxy aluminum aminoacetate tablets q.2.H. at night. Pamine was also used in three; tincture of belladonna was used in one because of the atony produced by Pamine. Only one case was placed on an uncomplicated ulcer regime after relief of obstruction. The remaining four had a gradual increase of diet until they received hourly skimmed milk and soft boiled eggs t.i.d., and cereal t.i.d. The intake was maintained without gastric distention until day of operation.

Results

The dosage of dihydroxy aluminum aminoacetate required to produce "free achlorhydria" varies from gm. 2 q.2.H. to gm. 3 q.2.H. in combination with

‡l-hyoscyamine was supplied by the Kremers-Urban Company, Milwaukee, Wisc., as the sulfate in 0.5 mg. tablets.

anticholinergic drug (Table I). The average dose of l-hyoscyamine sulfate and Pamine was 1 mg. q.6.H. and 2.5 mg. q.6.H. respectively. The patients with hemorrhage required no increase in dosage of either medication. Two cases deserve special attention. L.W. (Table I) required only 2 gm. of Alglyn q.2.H. at night to produce essentially "free achlorhydria", pH 3.6, and to heal the ulcer niche in 13 days. L.G. (Table I) required Alglyn q.2.H. and Pamine 10 mg. q.4.H. to produce a fasting pH of 3.6. When 45 c.c. of aluminum hydroxide-milk of magnesia mixture (4:1) was given q.1.H. and Pamine 10 mg. q.4.H. a pH of 2.5 was obtained. In this patient, the proven antacid, aluminum hydroxide-milk of magnesia mixture (4:1) was less efficient. In view of past experience and these values it is thought that the necessity for the hourly medication is not due to any ineffectiveness of Alglyn as an antacid, but is due to the rapid emptying of gastric contents.

When dihydroxy aluminum aminoacetate tablets only were given at the beginning of treatment, pain relief was rapid in the majority of cases. Without exception ulcer pain was amenable to therapy. Table II illustrates the time required to achieve complete freedom from pain. Of the 70 patients having pain at the onset of therapy, 50 (71.4 per cent) had relief within three days; 60 (85.7 per cent) in five days. The clinical healing time could only be determined in those cases having a demonstrable ulcer niche. This occurred in 16 (23.9 per cent) of the 67 patients with duodenal ulcer. The average healing time for the 16 duodenal craters was 14.8 days with a range of 7 to 35 days (Table III). Each patient was x-rayed (using a compression cone and filming fluoroscope), at weekly intervals until the niche disappeared. The healing time in this series is almost identical to the healing time average of 15 days for 506 duodenal ulcers reported by Rossett et al[2].

Further proof of healing was furnished when only scarring without inflammation was found in seven patients who had a subtotal gastric resection after 24 days of therapy. There were two patients treated previously with the same regimen by using aluminum hydroxide gel-milk of magnesia mixture (4:1). In both (Q.E. and J.B., Table I), the time for pain relief and ulcer healing was almost identical to that obtained with the present therapy.

Ten of the gastric ulcers were prepyloric. A niche was demonstrated in 4, and marked narrowing of the antrum was noted in 5. The tenth case was treated after perforation when the x-ray picture was not conclusive but pain was acute. The ulcer was confirmed later when a subtotal gastric resection was done. Three uncomplicated prepyloric niches measuring 2 x 1½ cm., 1½ x 1½ cm. and 1 x 1 cm. completely healed in 21, 19 and 24 days respectively. Two of these patients met the indications for surgery and a subtotal gastric resection was performed. In both, scarring was noted at the junction of the duodenal bulb and the stomach. No inflammatory process was present grossly. In one, the ulcer area was seen in the removed gross specimen. Microscopically, only scar tissue com-

TABLE I

ACHIEVEMENT OF "FREE ACHLORHYDRIA"

Name	Age	Alglyn (gm.)	l-Hyoscyamine (mg.)	Amt. (c.c.)	Fasting pH		Alglyn (gm.)	Pamine (mg.)	Amt. (c.c.)	Fasting pH
LW	64	2q2H	None	10	3.6		2q2H	None	10	3.6
JL	43	2q2H	0.5q6H	10	6.1					
MC	28	2q2H	1.0q6H(DC)	20	4.0		2q2H	5q6H	50	4.7
AR	22	2q2H	1.0q4H	30	4.9					
EB	48	2q2H	1.0q4H	30	6.1					
TR	43	2q2H	0.5q4H	10	5.0					
JH	36	2q2H	1.0q6H(DC)	10	3.2		2q2H	5q6H	30	6.3
JK	24	2q2H	0.5q4H	15	4.8					
CR	56	2q2H	0.5q6H	5	5.1					
JB	62	2q2H	0.5q6H	30	5.8					
RK	19	2q2H	0.5q4H	50	6.6					
JB	54	2q2H	1.0q6H	10	6.2					
"	"	"	None	20	4.0					
MMcK	44						2q2H	10q4H	20	4.2
JH	43						2q2H	5q6H	15	4.2
QE	58						2q2H	2.5q6H	5	5.5
CC	46						2q2H	2.5q6H	15	5.5
AD	33						2q2H	2.5q6H	10	3.8
JG	58	2.5q2H	1q6H	90	3.6					
AP	35	2.5q2H	1q6H	10	3.7					
HB	34	2.5q2H	1q6H	15	4.8					
LP	61	3q2H	1q4H(DC)	—	Pos X	Duodenal ulcers	3q2H	10q6H	10	5.8
RP	31	3q2H	1q4H	30	4.8					
HR	61	3q2H	0.5q6H	20	4.0		3q2H	10q6H(DC)	—	5.1
JK	56	3q2H	1q4H(DC)	20	4.7					
JM	32	3q2H	1q6H(DC)	90	4.1		3q2H	5q6H	100	4.5
CD	29	2.5q2H	1q6H	10	3.6		3q2H	10q4H	50	3.4
JW	66						3q2H	5q6H	10	6.6
CT	43						3q2H	5q8H	10	4.2
LG	43						2q1H	10q4H	10	3.6y
JL	43	2q2H	1q6H	15	3.5					
HL	55	2q2H	1q4H	30	6.1					
EM	58	2q6H	1q6H	—	6.1					
WB	64	3q2H	None	30	4.5	Gastric ulcers	3q2H	5q6H(DC)	500	3.9
JC	56	3q2H	1q4H	25	5.5					
RW	36						3q2H	5q6H	25	5.1

X—Positive reaction with Topfer's reagent.

Y—With Aluminum Hydroxide-Magnesium Hydroxide (4 parts to 1 by volume), 45q1H, pH 2.5.

DC—Drug was discontinued.

•This table shows the medication used in the first 35 cases. The remaining 45 cases are similar except for the reduction of Pamine to an average of 2.5 mg. q6H.

pletely covered with epithelium was seen. The fourth prepyloric niche was associated with obstruction and mild hemorrhage. Pain was completely relieved in 9 days, obstruction in 7 days, and the niche completely healed in 21 days. This patient refused an operation. The patient with the perforated prepyloric ulcer was transferred to the Medical Service one month after his perforation. Postoperatively he had an acute ileus and was treated with intestinal decompression for 6 days. Thereafter he received an ulcer diet with no antacids until he was transferred to the Medical Service with acute epigastric pain still present. It is, therefore, interpreted that he had an acute active ulcer when therapy was begun. He received intensive therapy for 28 days and then was transferred to the Surgical Service where a subtotal gastric resection was performed. The

TABLE II

TIME REQUIRED TO RELIEVE PAIN

Days	Duodenal	Gastric
Less than 1	10	3
1	12	2
2	13*	2
3	9	3
4	8	0
5	3	0
6	0	1
7	1	0
9	0	2
10	1	0

The remainder had no pain at onset of therapy.
*One patient had no pain but acute nausea.

pathological diagnosis was "healed gastric ulcer". Four patients with gastric ulcer demonstrable only as antral narrowing showed relief of spasm and widening of the antrum in 7 to 21 days. The fifth also showed obstruction, and a subtotal gastric resection was done after 26 days of treatment. Microscopic examination showed scarring and almost complete epithelization.

Six of the gastric ulcers were on the lesser curvature of the *pars media*. The size varied from 1-2 cm. Five healed completely. The sixth received only 18 days of treatment before a subtotal gastric resection was done before healing due to domestic urgency. The operation was advised because of hemorrhage. The ulcer measured less than 1 cm. in diameter. Microscopically the scar was firm with epithelization. The healing time of the gastric niches by x-ray or

gastroscopy varied from 14-26 days (average 20.6 days). In two, gastroscopic healing was 7 days longer than the roentgenographic healing.

The jejunal ulcer developed in a 60-year old male who had a subtotal gastric resection performed 3 years previously. While receiving ACTH for

TABLE III

TIME REQUIRED FOR CRATER HEALING (DAYS)

Name	Duodenal	Gastric
A.R.	10	
E.B.	15	
C.R.	7	
L.W.	13	
C.D.	14	
J.W.	7	
C.T.	14	
J.H.	14	
Q.E.	19	
J.B.	35	
V.W.	14	
G.D.	12	
R.H.	13	
W.S.	18	
R.R.	17	
C.C.	21	
H.L.		21
J.C.		19
W.B.		21
J.K.		24
T.C.		24
J.S.		*
R.R.		25
J.M.		17
W.L.		16
J.H.		14

*Operation before complete healing.

rheumatoid arthritis, pain and melena developed. All bleeding had ceased when the patient was first examined. The jejunal ulcer measured 3 cm. in diameter and was surrounded by edematous mucosa. Within 1 week while receiving only a convalescent ulcer diet and Alglyn 2.5 mg. between meals and q.2.H. at night, all edema disappeared. The niche was not noted after three weeks of treatment.

Only eight of the 80 patients had any objections to the Alglyn tablets. Within the first 3 days of treatment seven of these complained of slight nausea after chewing the pills, and the eighth complained of a "bad taste". These complaints were relieved completely in 7 of the 8 by having the patient take

TABLE IV

UNDESIRABLE EFFECTS OF THERAPY

Drug	No. Cases	Constipation*				Urinary			Mydriasis			Xerostomia†			Psychogenic
		Normal	Mild	Mod.	Severe	Hesitancy Min.	Hesitancy Mod.	Retention	Min.	Mod.	Marked	Min.	Mod.	Marked	
Alglyn	5	2	1	2	0	0	0	0	0	0	0	0	0	0	0
Alglyn plus Pamine	54	21	17	12	4	13	5	1	6	10	2	10	8	3	0
Alglyn plus l-hyoscyamine sulfate	25	17	5	3	0	20	5	0	9	15	1	16	3	3	3

*Normal—No complaint or 1 enema or 1 ounce $Mg(OH)_2$ during 21 days of therapy.
Mild—Need for laxative or enema on 2-5 occasions.
Moderate—Need for laxative or enema every 2-3 nights.
Severe—Slight impaction or need for laxative or enema nightly.
†Not recorded in 2 cases.

the medication with milk in place of water. One of these eight patients had previously been treated with aluminum hydroxide gel that was discontinued because of nausea and vomiting.

When using aluminum preparations, and especially in combination with anticholinergic drugs, constipation can be a serious problem. In the five patients treated with Alglyn alone (Table IV), two had no constipation requiring no enemas or milk of magnesia; one required mineral oil suspension on two occasions; two had moderate constipation. The patient taking Alglyn, gm. 2 q.1.H. at night, and Pamine, 10 mg. q.4.H., had no constipation. The remainder of

the patients had no more severe constipation than any group treated with anticholinergic drugs alone. The most constipation occurred in those who had noted chronic constipation prior to entrance to the hospital.

The other common side-effects of anticholinergic drugs were xerostomia, urinary hesitancy, mydriasis, and psychogenic irritability. Fifty patients had no complaint of mydriasis and 46 noticed no xerostomia. The urinary hesitancy was minimal in the majority of cases. In only one case did pyuria develop, necessitating the discontinuance of the drug. In the large dosage employed, of the 25 patients receiving l-hyoscyamine sulfate, it was discontinued in five patients; one for tachycardia developing while walking, one for dizziness, one for severe gastric hypotonia, and three for toxic changes consisting of nervous irritability. In 140 patients treated with 1.25 mg. of l-hyoscyamine sulfate daily, it had to be discontinued in only one 74-year old patient for early hallucination without disorientation[4]. Pamine was substituted in all these cases except one with toxic psychogenic reaction, and none of the symptoms returned. Pamine was discontinued in four of the 38 patients receiving this drug; one with the complaint of abdominal bloating that did not return when l-hyoscyamine sulfate was substituted, the second for cystitis, in the third for splenic flexure syndrome, and in the fourth for gastric atony. Anticholinergic drugs were discontinued completely in these two patients.

Comment

There is a definite convenience of tablet medication over liquid gel preparations but convenience should never be gained at the expense of the effectiveness of therapy. From the *in vitro*[1] evaluation and the result of this series, the tablet form of Alglyn (dihydroxy aluminum aminoacetate) appears as effective in the therapy of peptic ulceration as the liquid aluminum hydroxide gel preparations.

The average healing time of 14.8 days for duodenal craters and 20.6 days for gastric craters is almost identical to the average healing time of 15 days for duodenal ulcers and 16.9 days for gastric ulcers reported by Rossett et al[2]. These results are significant when compared with a large series of patients treated with a Sippy diet, atropine, and sedation by Cummings, Grossman and Ivy[3]. Their average healing time was 40 days (range of 12 to 230 days) for 63 duodenal craters and 42 days (range of 18 to 68 days) for 6 gastric craters. A series of 80 patients is small, but the consistent results obtained and the achievement of verified "free achlorhydria", indicates a larger series would not differ significantly.

In this study Alglyn was not discontinued because of any side-effects. Table IV shows the degree of constipation, urinary disturbance and psychogenic irritability produced by the anticholinergic drug. Constipation and urinary disturbance occurred in any age group, but was most severe in those over 50. All attempts should be made to produce "free achlorhydria" in those patients over

60 years of age without the use of anticholinergic drugs. Whenever anticholinergic drugs are used, particularly in patients with an anxiety reaction, there should be constant observation for personality or definite psychiatric changes. Although large doses of anticholinergic drugs were used in the first half of this study, it appears that l-hyoscyamine 1 mg. q.6.H. and Pamine 5 mg. q.6.H. should be the maximum dosage.

In the management of many patients the available anticholinergic drugs are a valuable adjunct to antacid therapy. There is, however, a need for an improved, longer acting anticholinergic agent.

Summary

A series of 80 patients with peptic ulceration treated with the tablet form of the relatively new aluminum compound, dihydroxy aluminum aminoacetate, NNR (Alglyn), is presented.

This *in vivo* study confirms the conclusions of the *in vitro* evaluation[1] of the effectiveness of the tablet form of dihydroxy aluminum aminoacetate, NNR (Alglyn), as an antacid. The results closely approximate those obtained when the liquid antacid aluminum hydroxide-milk of magnesia mixture (4 parts to 1 by volume) is used.

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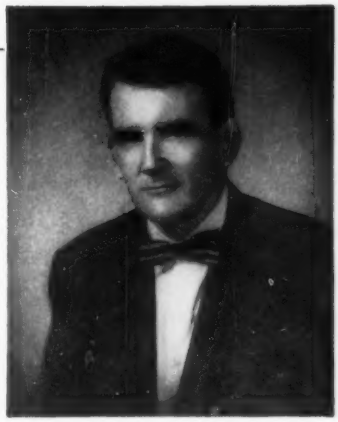

President's Message

The 1955 Chicago Convention was the most successful in recent years, as measured by the quality of papers presented and attendance at the program and course. Our 1956 New York Convention will be a homecoming for the College. Dr. Frank Borrelli, our competent 2nd Vice-president, will direct the program and the course in his usual capable and experienced manner.

Dr. Arthur Kirchner is Chairman of our Membership Committee for the coming year. The increasing recognition of and interest in the American College of Gastroenterology makes his duty one of selection rather than solicitation. As you are aware, all candidates must be processed through the governors of their respective states and through the Credentials Committee prior to nomination.

Chapters were an integral part of the National Gastroenterological Association. During the infancy of the American College of Gastroenterology, it was considered best to temporarily de-emphasize local affiliations. It is the opinion of the majority of our fellows and members, however, that local societies or chapters must be encouraged and inducted into our organization. State societies of gastroenterology should be formed in areas where our membership is new and expanding. Our Board of Governors is already studying the best method of cementing our relationship with the east coast chapters that gave us birth.

Finally, Dr. Louis Ochs, Chairman of our Board of Governors, is planning a regional meeting in New Orleans on 8 April 1956. Inauguration of the Abraham Levin Memorial Lectureship will be a highlight of the program.

I. J. Nif

NEWS NOTES

College Regional Meeting

A regional meeting of the American College of Gastroenterology will be held in New Orleans, La. The one-day session will take place at the Louisiana State University School of Medicine on Sunday, 8 April 1956.

The program for the session is being arranged by Dr. Louis Ochs, Jr., assisted by the governors of the College for the southern region.

Further details concerning the program will be found in the next issue of the journal.

Members of the medical profession are cordially invited to attend the session.

Annual Meeting Board of Trustees

The Annual Meeting of the Board of Trustees of the American College of Gastroenterology was held on 23 October 1955 at The Shoreland in Chicago, Ill.

Dr. Sigurd W. Johnsen, Chairman, presided and routine administrative matters were presented and properly disposed of.

The College was advised of the deaths of Drs. William L. Wolfson, Philip Ladin, Patrick M. Moriarty and Sylvan S. Scholpp. Letters of condolence were sent by the Secretary.

Dr. Lynn A. Ferguson, President, presented his report of the activities in the past year and presented several matters for consideration during the coming year. He thanked the officers, members of the board and the committee chairmen for their help during the past year.

Dr. Johnsen also expressed the appreciation of the Board and the committees for the work which Dr. Ferguson had done in the past year.

Dr. Elihu Katz, Treasurer, submitted his report and an audited statement for the nine months ending 30 September 1955, which report was accepted with thanks.

The Secretary-General, Dr. Roy Upham, was unable to attend in person but a message was read from him and the Secretary was instructed to send a return message expressing the regrets of the Board at his inability to be present.

Dr. William W. Lermann, Chairman of the Committee on Finance and Budget, was also unable to be present and his written report on the financial statement and the estimated budget for 1955-56 was read.

The budget was presented as adopted and those present were advised that with its adoption the financial affairs of the College would now be on a fiscal rather than on a calendar year.

The Executive Secretary, Mr. Daniel Weiss, presented a written report of the activities of his office and requested closer cooperation from committee chairmen in the work being done.

The Board voted to require that carbon copies of all official correspondence sent out by committee chairmen and officers be furnished to the executive office for record purposes.

A written report from Dr. Arthur A. Kirchner, Chairman of the Program Committee, called attention to the work accomplished in preparing a program and also urged the adoption of the previously voted motion.

Dr. Kirchner was thanked for his work in preparing the excellent scientific program for the convention.

Dr. John E. Cox, Chairman of the Committee on Public Relations, reported on the publicity and the work of the professional public relations counsel.

Dr. Samuel Weiss, Editor of THE AMERICAN JOURNAL OF GASTROENTEROLOGY and Chairman of the Editorial and Publication Committee, reported that the number of pages in the journal had been increased because of the large number of papers which were on hand for publication. He further reported that the committee had met and was planning a rather ambitious program for the coming year.

Dr. H. Necheles, Chairman of the Research Committee, reported that the Ames Award Lecture would be presented by Dr. George B. Eusterman of the Mayo Clinic. The first prize for the best paper submitted by a resident was to be awarded to Dr. Robert S. Kaplan of Los Angeles, Calif. The award for the best paper published in THE AMERICAN JOURNAL OF GASTROENTEROLOGY in the past year was to be given to Dr. M. E. Steinberg of Portland, Oreg.

A voluntary contribution of $10.00, to be added to the annual bill for dues, had been approved previously and Dr. Necheles suggested that this be placed on the statement this year in order to provide funds for research. This was approved.

In the absence of Dr. C. Wilmer Wirts, Chairman of the Committee on Graduate Education, Dr. Ferguson reported for him pointing out the difficulties encountered by having two different chairmen for the Convention and the Postgraduate Course. The program for the Course which Dr. Wirts and his committee are presenting is an exceptional one despite the handicap mentioned. It was suggested that in the future only one chairman be appointed for both parts of the program and this was approved.

Dr. James T. Nix, Chairman of the Committee on Revision of Constitution and By-laws, reported that the committee had met and had certain specific recommendations which it desired to present to the Board for consideration. These were tabled until the spring meeting of the Board.

Dr. Sigurd W. Johnsen, Chairman of the Nominating Committee, reported that the slate of officers had been mailed to the Fellowship together with biographical data on each candidate. He asked the Board to approve the con-

tinuation of the practice of submitting this biographical data which approval was granted.

It was proposed that the state of California be divided into a northern and southern section for the purpose of governorship which recommendation was approved for presentation to the Fellowship.

Dr. Frank J. Borrelli, Chairman of the Credentials Committee, reported that his committee had been functioning in carefully appraising and evaluating applications for election and advancement. He proposed a concerted drive for new membership be considered.

Dr. Henry Baker, Chairman of the Committee on Hospital Relationships, reported that the Committee found a definite lack of residencies in gastroenterology and suggested that steps be taken to cooperate with other committees in a program to establish more of them.

Dr. William C. Jacobson, Chairman of the Committee on Convention Arrangements, reported that all business sessions and the convocation would be held on Sunday in order to expedite the program. If this arrangement proves satisfactory, it would be continued.

Arrangements for the banquet called for a minimum of speaking and a maximum of entertainment.

Dr. Arthur A. Kirchner submitted a written report of the special committee on insurance, recommending that a poll of the membership be taken to determine whether group insurance is desired.

As Chairman of the special committee on placement, Dr. Kirchner presented ways and means of preparing a location roster.

The Board of Trustees voted to require all elected and advanced Fellows to attend the convocation in person either the year of their election or at the next two years in order to receive their certificates.

Dr. Johnsen extended to the Board his deepest appreciation for their cooperation and thanked the Board for the opportunity of having been its Chairman and an officer of the organization for these many years. His term of office was up under the provisions of the Constitution and he was not eligible for re-election this year.

The Board gave Dr. Johnsen a standing vote of thanks for his unstinting contribution and devotion to the work of the College.

Second Annual Convention
American College of Gastroenterology

The Second Annual Convention of the American College of Gastroenterology was held at The Shoreland in Chicago, Ill., and a most exceptional pro-

gram of scientific papers was presented. The attendance was highly satisfactory and far exceeded that of the previous convention in Chicago.

At the Convocation of the College on Sunday evening, 23 October 1955, certificates of election and advancement were presented to those newly elected to and advanced in the College and several Honorary Fellows.

The audience heard an inspiring address on "Medicine's Responsibility in the Conservation of Human Resources" by Dr. Ross T. McIntire, Executive Director of the International College of Surgeons. The invocation was delivered by Rabbi Norman Siegel, Hyde Park Hebrew Center and the benediction by the Rev. William N. Weaver, assistant dean of the Federated Faculties of the School of Religion, University of Chicago. Dr. Maurice Hoeltgen, President of the Chicago Medical Society welcomed those attending the sessions.

On Monday, 24 October 1955, those present enjoyed an excellent luncheon and an address by Dr. Morris Fishbein, former editor of the *Journal of the American Medical Association*. This was again sponsored by Burton, Parsons and Company of Washington, D. C. to whom we extend our sincere appreciation and thanks.

At the annual banquet on Tuesday evening, 25 October 1955, Dr. James T. Nix of New Orleans, La. was invested with the insignia of office by the outgoing President, Dr. Lynn A. Ferguson of Grand Rapids, Mich. Dr. Nix presented Dr. Ferguson with a Past-President's key. Mr. Charles F. Miles, President of Ames Co., Inc., Elkhart, Ind. made the presentation of the Ames Awards.

Annual Meeting of the American College of Gastroenterology

The Annual Meeting of the American College of Gastroenterology was held at The Shoreland in Chicago, Ill. on Sunday, 23 October 1955.

Dr. Lynn A. Ferguson, President of the College presided. He presented a report of the activities of the College during his administration and thanked all those who worked with him for their cooperation and efforts.

The Treasurer, Dr. Elihu Katz, presented the financial statement for the calendar year ending 31 December 1954 as well as a statement for the first nine months of 1955. He reported that although several of the membership had not yet paid their dues for the current year sufficient funds were available for the balance of the year as allotted in the budget.

Dr. Frank J. Borrelli, Chairman of the Credentials Committee reported an increase in membership. The total membership of the College was 815 as follows: Honorary Fellows, 26; Life Fellows, 29; Fellows, 297; Associate Fellows, 143 and Members, 342. This did not include applications pending before the Credentials Committee.

Dr. Arthur A. Kirchner, Chairman of the Program Committee reported that this year's program reflected an increase in the number of papers being presented by the membership of the College and it is hoped that this trend will continue.

Dr. John E. Cox reported as Chairman of the Committee on Public Relations about the publicity for the Convention.

The Editor, Dr. Samuel Weiss, reported on the status of the journal and thanked the members of the Editorial Board, Drs. James A. Ferguson, Milton J. Matzner, Michael W. Shutkin and Joseph R. Van Dyne, as well as all of the members of the abstract staff, for their fine work during the year. He presented the College with a check for $1,000 making a total of $4,000 in surplus journal funds thus far presented in 1955.

In the absence of Dr. Nechcles, Chairman of the Research Committee, Dr. Ferguson reported on the Ames Awards and the voluntary contribution to the research fund which is to be placed on the bill for annual dues.

Dr. Ferguson also reported for Dr. C. Wilmer Wirts, Chairman of the Committee on Graduate Education concerning the Postgraduate Course. He personally thanked Dr. Edward J. Krol of Chicago for his great help with the program and the Course.

Dr. James T. Nix reported that the committee on Revision of Constitution and By-laws had approved an amendment to the By-laws to be presented to the Fellowship for adoption under new business. He further stated that the committee had met and considered certain recommendations to be presented as amendments the following year.

Dr. Sigurd W. Johnsen, as Chairman of the Nominating Committee presented the report of his committee.

Under new business the proposed amendment to the By-laws pertaining to the qualifications of Fellows was tabled after considerable discussion.

Governorships for the states of Alabama, Indiana, Iowa, Kentucky, Mississippi, Missouri, Texas, and for the Province of Quebec, the District of Columbia and for the northern section of California were voted.

The Secretary reported that no additional nominations for office had been received and upon motion duly made, seconded and carried, he was instructed to cast one vote for the slate presented by the Nominating Committee.

Under good and welfare, the site of a regional meeting for 1956 was presented. Dr. Michael W. Shutkin spoke about the scientific exhibits and urged greater participation next year. Dr. Maxwell R. Berry of Atlanta, Ga. inquired concerning the status of groups which desired affiliation. Dr. Louis Ochs, Jr. advised that the group in New Orleans would like to establish a lecture to be given in the name and in honor of Dr. A. L. Levin, the deceased founder of the New Orleans group.

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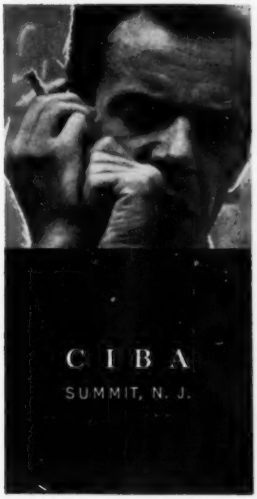

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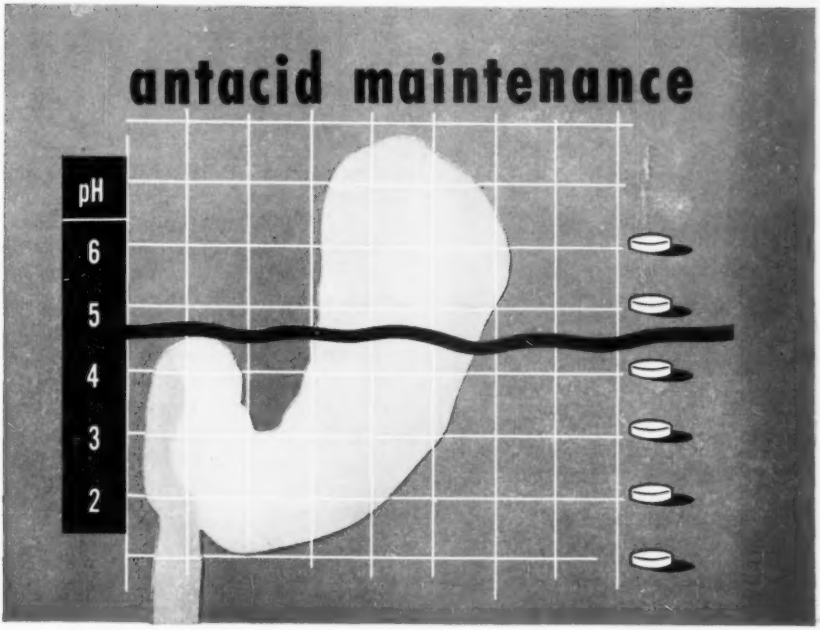

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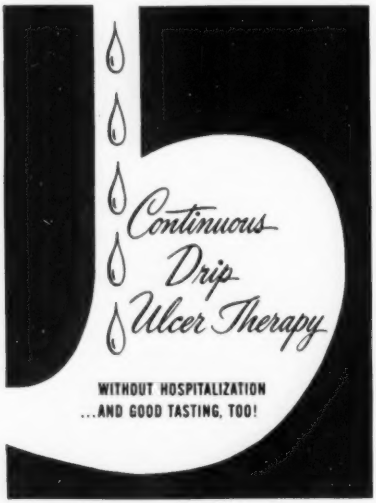

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*Steigmann, F., and Goldberg, E.: Ambulatory Continuous Drip Method in the Treatment of Peptic Ulcer, Am. J. Digest. Dis. *22*:67 (Mar.) 1955.

†Mg trisilicate 3.5 gr.; Ca carbonate 2.0 gr.; Mg oxide 2.0 gr.; Mg carbonate 0.5 gr.

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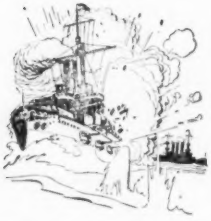

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*Schaefer, F. H.: Ohio State M. J. 51:347 (April) 1955.
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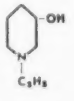

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